World Journal of Gastroenterology

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DOI: 10.3748/wjg.v20.i29.9828

World J Gastroenterol 2014 August 7; 20(29): 9828-9849
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (5): Colorectal cancer

Genetic predisposition to colorectal cancer: Where we stand and future perspectives

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Author contributions: Valle L drafted and revised the manuscript and gave final approval of the version to be published.
Supported by The Spanish Ministry of the Economy (State Secretariat for Research, Development and Innovation), grant SAF2012-38885 and Ramón y Cajal contract; L'Oréal-UNESCO "For Women in Science"; and the Scientific Foundation Asociación Española Contra el Cáncer
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Received: October 16, 2013 Revised: February 10, 2014
Accepted: April 2, 2014
Published online: August 7, 2014

Abstract

The development of colorectal cancer (CRC) can be influenced by genetic factors in both familial cases and sporadic cases. Familial CRC has been associated with genetic changes in high-, moderate- and low-penetrance susceptibility genes. However, despite the availability of current gene-identification techniques, the genetic causes of a considerable proportion of hereditary cases remain unknown. Genome-wide association studies of CRC have identified a number of common low-penetrance alleles associated with a slightly increased or decreased risk of CRC. The accumulation of low-risk variants may partly explain the familial risk of CRC, and some of these variants may modify the risk of cancer in patients with mutations in high-penetrance genes. Understanding the predisposition to develop CRC will require investigators to address the following challenges: the identification of genes that cause uncharacterized hereditary cases of CRC such as familial CRC type X and serrated polyposis; the classification of variants of unknown significance in known CRC-predisposing genes; and the identification of additional cancer risk modifiers that can be used to perform risk assessments for individual mutation carriers. We performed a comprehensive review of the genetically characterized and uncharacterized hereditary CRC syndromes and of low- and moderate-penetrance loci and variants identified through genome-wide association studies and candidate-gene approaches. Current challenges and future perspectives in the field of CRC predisposition are also discussed.

Key words: Hereditary colorectal cancer; Familial colorectal cancer; High penetrance; Low penetrance; Cancer syndromes; Cancer susceptibility; Hereditary cancer genes; Risk variants; Heritability

Core tip: The risk of developing colorectal cancer (CRC) can have genetic influences, especially when there is a family history of the disease. Much of this genetic predisposition to develop cancer is already known, including high-penetrance genes, *i.e.*, those responsible for hereditary cases, and low-penetrance alleles, which are responsible for both sporadic and familial cases. However, despite recent developments in gene identification techniques, the genetic causes of many hereditary cases remain unknown. This review details the hereditary CRC syndromes and their genetic causes, the roles of low- and moderate-risk genetic factors in familial cases and the state-of-the-art in the identification of new causal genes.

Valle L. Genetic predisposition to colorectal cancer: Where we stand and future perspectives. *World J Gastroenterol* 2014; 20(29): 9828-9849 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i29/9828.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i29.9828

BACKGROUND

Colorectal cancer (CRC) is the third most common cancer, accounting for 10% of all cancers and affecting approximately 1 million people worldwide every year[1]. Although most cases of CRC are thought to be sporadic, crude estimates indicate that familial CRC, defined by the presence of two or more first-degree relatives affected with CRC, accounts for more than 20% of all cases[2-4]. All CRC syndromes caused by known high-penetrance CRC genes collectively account for 2%-6% of all cases of CRC. For decades, gene-identification strategies such as genome-wide linkage studies or studies involving high-throughput sequence capture methods and next-generation sequencing technologies have sought to identify new high-penetrance genes that could explain the aggregation of CRC in high-risk families. Despite this technological progress, the genetic etiology of familial cancers such as familial colorectal cancer type X (fCRC-X) or serrated polyposis (SP) remains unknown.

For years, scientists have hypothesized that the heritable nature of CRC might be associated with the co-inheritance of multiple low-risk variants[2,3] that may interact with environmental factors. This hypothesis was supported by the identification of single-nucleotide polymorphisms (SNPs) localizing to different genomic regions that influence the risk of CRC[5]. The risk of CRC associated with each of the variants is individually low; however, the combined effect of these variants could significantly contribute to disease burden, especially given the high prevalence of these variants in the general population. Moreover, the presence of these or other SNPs might modify the risk of cancer in families with mutations in known predisposing genes such as those associated with lynch syndrome (LS)[6-8].

In this review, we present current knowledge on the genetics of inherited CRC syndromes and of moderate- and low-risk variants of CRC; we also describe the approaches currently being used to understand the genetic causes of uncharacterized hereditary cases of CRC. Current challenges and future perspectives are discussed. Clinical issues such as surveillance, prophylactic and preventive measures, treatments and genetic counseling are not reviewed.

GENETICALLY CHARACTERIZED INHERITED COLORECTAL CANCER SYNDROMES

A summary of the main genes associated with hereditary cancer syndromes is provided in Table 1; information on the modes of inheritance of these syndromes, the types of mutations identified in patients with these syndromes and the molecular features of tumors are also presented.

LS

LS (MIM No. 120435) is an autosomal dominantly inherited disorder caused by germline mutations or epimutations in a DNA mismatch repair (*MMR*) gene (*MLH1*, *MSH2*, *MSH6* or *PMS2*).

Carriers of a heterozygous mutation (or epimutation) in a *MMR* gene are at high risk of developing CRC and at increased risk of developing malignancies at extracolonic sites such as the endometrium, ovary, stomach, small bowel, hepatobiliary tract, urinary tract, brain and skin[9]. A detailed description of the clinical and pathological features of LS is provided in Table 2. Of note, biallelic deleterious germline mutations in *MMR* genes lead to a constitutional mismatch repair-deficiency, a syndrome characterized by a broad spectrum of early-onset malignancies such as hematologic neoplasms and brain and LS-associated tumors and a phenotype that resembles the phenotype associated with neurofibromatosis type 1[10].

Mismatch repair genes behave like tumor suppressors; cancer arises when a second hit (mutation, deletion or CpG island methylation) somatically inactivates the wild-type allele in a target cell (*e.g.*, a cell of the colonic epithelium)[11-14]. The complete inactivation of the corresponding *MMR* gene in the tumor causes a marked reduction in MMR function, which results in microsatellite instability (MSI)[15,16].

The identification of *MMR* gene mutation carriers is critical for improving cancer surveillance and the effectiveness of preventive measures[17,18]. Before *MMR* genes and their causal role in hereditary CRC cancer were identified, the International Collaborative Group on hereditary non-polyposis colorectal cancer established the Amsterdam criteria in 1990. These criteria, the first clinical criteria used to define hereditary non-polyposis colorectal cancer, were used to identify families for research studies[19] and subsequently modified (Amsterdam Ⅱ) to include extracolonic LS-related cancers[20]. However, the Amsterdam criteria failed to identify a large portion of *MMR* gene mutation carriers[21,22]. The Bethesda guidelines, which were less restrictive and had a sensitivity greater than 90% but a specificity of only 25%, were later defined[23,24].

Tumor testing is used to enhance the predictive power of clinical selection features and to identify the genes most likely to have a causative germline mutation. Standard tumor testing for LS involves the study of MSI and/or immunohistochemistry to detect the protein products expressed by MMR genes. However, because 10%-15% of sporadic CRCs also exhibit MSI[21,25-28], the detection of somatic *MLH1* promoter methylation and somatic *BRAF* V600E mutations in patients with a MMR deficiency could help identify tumors that are more likely to be sporadic[29]. If the results of these tests suggest a diagnosis of LS, then germline molecular genetic testing of *MMR* genes is performed. The National Comprehensive Cancer Network has established unified CRC screening strategy guidelines (http://www.nccn.org).

In recent years, the concept of population-based universal screening for LS has gained strength among researchers and clinicians. The identification of individuals who are at increased risk of hereditary cancer allows for the possibility of specialized surveillance and early can-

Table 1 Hereditary colorectal cancer genes, major associated syndromes, modes of inheritance, types of mutations identified and specific molecular characteristics of associated tumors

Gene	Syndrome	Inheritance	Mutations reported	Tumor molecular features
MLH1	Lynch syndrome	Autosomal dominant	Point mutations[1] Large rearrangements CpG island methylation	MMR deficiency (MSI)
MSH2	Lynch syndrome	Autosomal dominant	Point mutations Large rearrangements CpG island methylation[2]	MMR deficiency (MSI)
MSH6	Lynch syndrome	Autosomal dominant	Point mutations Large rearrangements	MMR deficiency (MSI)
PMS2	Lynch syndrome	Autosomal dominant	Point mutations Large rearrangements	MMR deficiency (MSI)
EPCAM	Lynch syndrome	Autosomal dominant	Large rearrangements[2]	MMR deficiency (MSI)
APC	(Attenuated) familial adenomatous polyposis	Autosomal dominant *De novo* mutations Mosaicisms	Point mutations Large rearrangements ASE (deep-intronic and promoter mutations)	-
MUTYH	*MUTYH*-associated polyposis	Recessive	Point mutations Large rearrangements	Base excision repair deficiency: KRAS c.34G>T
POLE	Polymerase proofreading-associated polyposis	Autosomal dominant	Point mutations (exonuclease domain)	Hypermutated: excess of G:C>T:A transversions
POLD1	Polymerase proofreading-associated polyposis	Autosomal dominant	Point mutations (exonuclease domain)	Hypermutated: excess of G:C>T:A transversions
GREM1	Hereditary mixed polyposis	Autosomal dominant	40-kb upstream duplication[3]	-
SMAD4	Juvenile polyposis	Autosomal dominant	Point mutations Large rearrangements	-
BMPR1A	Juvenile polyposis	Autosomal dominant	Point mutations Large rearrangements	-
STK11	Peutz-Jeghers	Autosomal dominant	Point mutations Large rearrangements	-
PTEN	*PTEN* hamartoma tumor[4]	Autosomal dominant	Point mutations Large rearrangements Promoter	-

[1]Point mutations include missense, non-sense, frameshift and splice-site mutations and small intragenic deletions/insertions; [2]*MSH2* germline CpG island methylation occurs secondary to *EPCAM* deletions; [3]Founder Ashkenazi mutation; [4]*PTEN* hamartoma tumor syndrome includes Cowden, Bannayan-Riley-Ruvalcaba, *PTEN*-related Proteus and Proteus-like syndromes. ASE: Allele-specific expression; MMR: DNA mismatch repair; MSI: Microsatellite instability.

cer detection, potentially resulting in decreased disease-specific mortality[30]. Because the prevalence of LS in the population is relatively high (approximately 3% of all diagnosed cases of CRC) and because surveillance strategies aimed at cancer prevention and early detection in LS patients have proven benefits[17], there is a clear rationale for exploring universal LS screening at the population level. Moreover, universal screening for LS is feasible, as LS tumors exhibit MMR deficiencies that can easily be identified with a simple PCR-based assay for MSI or by immunohistochemistry to identify the loss of expression of a MMR protein. Several studies have demonstrated the feasibility of this approach from a research and a clinical perspective[31-34]. In fact, in 2009, the Evaluation of Genomic Applications in Practice and Prevention recommended that all patients newly diagnosed with CRC be screened for LS through PCR-based MSI testing or immunohistochemistry[35]. However, at the population level, significant challenges and barriers to the successful implementation of this screening process exist[36].

MLH1 and *MSH2* germline mutations, *MSH6* mutations and *PMS2* mutations account for approximately 90%, 7%-10% and less than 5% of mutations in families with LS, respectively[37-40]. Germline deletions in *EPCAM* that inactivate *MSH2* (*via* the methylation of CpG islands) occur in approximately 1% of LS cases[41,42]. Finally, the constitutional inactivation of *MLH1* by CpG island hypermethylation also causes Lynch syndrome; for this reason, *MLH1* promoter methylation screening could be useful in individuals who have experienced a loss of MLH1 expression in their tumors and who have a negative germline sequence screen[43-45]. Large deletions and genetic rearrangements account for 20%, 5%, 20%, 7% and 100% of mutations in *MSH2*, *MLH1*, *PMS2*, *MSH6* and *EPCAM*, respectively[40,46-49].

In some populations, recurrent mutations (*i.e.*, those occurring repeatedly *de novo*) or ancestral (founder) mutations can change the aforementioned proportions; preliminary screening for these mutations can facilitate the molecular diagnosis of LS[50-54].

For years, researchers have sought to identify genetic modifiers that could affect the risk of cancer in *MMR* gene mutation carriers to explain the high variability in individual cancer risk among carriers. Identifying these modifying factors can enable an efficient stratification of mutation carriers based on their predicted risk and thereby offer a more appropriate clinical management strategy based on personalized surveillance programs. Initial at-

Table 2 Clinico-pathological characteristics of Lynch syndrome

Clinico-pathological characteristics
The onset of colorectal cancer (CRC) occurs at an early age (average 45 yr)
Predilection to develop proximal (right-sided) colon cancer
High risk of multiple primary colorectal tumors (synchronous or metachronous)
Specific pathological features of lynch syndrome-related colorectal tumors:
Poorly differentiated
Mucinous
Signet-cell features
Crohn's-like lymphocytic reaction
Excess of tumor-infiltrating lymphocytes
Increased survival (in patients with CRC)
Accelerated carcinogenesis
Increased risk of cancer at extracolonic sites:
Endometrium
Ovary
Stomach
Small bowel
Hepatobiliary tract
Pancreas
Upper uroepithelial tract
Brain (Turcot's syndrome)
Sebaceous adenomas, carcinomas and keratoacanthomas (Muir-Torre syndrome)

Table 3 Clinical characteristics of familial adenomatous polyposis

Clinical characteristics
Hundreds to thousands of colonic adenomatous polyps (on average beginning at age 16 yr)[1]
Colorectal cancer (100% penetrance if not treated; average age 39 yr)[1]
Other gastrointestinal polyps and malignant lesions:
Fundic gland polyps in the stomach
Adenomatous polyps in the stomach and small bowel
Periampullary carcinoma
Duodenal cancer
Congenital hypertrophy of the retinal pigmented epithelium (CHRPE)
Other less common manifestations:
Embryonal tumors (hepatoblastoma and medulloblastoma)
Pancreatobiliary carcinoma
Papillary thyroid carcinoma (especially cribriform-morular variant)
Adrenal cortical tumors
Gardner syndrome subtype (specific characteristics):
Colonic adenomatous polyposis
Desmoid tumors
Epithelial inclusion cysts
Osteoid osteomas
Supernumerary and/or impacted teeth
CHRPE
Turcot syndrome subtype (specific characteristics):
Colonic adenomatous polyposis
Tumors of the central nervous system (medulloblastoma)

[1]AFAP: Patients have 10-100 colorectal adenomas. Polyps develop preferentially in the proximal colon, and the onset of colorectal cancer (CRC) occurs 10-15 years later than in patients with classic familial adenomatous polyposis. The cumulative risk of CRC by age 80 years is estimated to be approximately 70%.

tempts to identify cancer risk modifiers in patients with LS were based on the study of candidate genes; however, few of these studies were validated in larger-sized populations[55]. With the arrival of genome-wide association studies (GWAS), researchers hypothesized that the common variants associated with the risk of CRC in the general population could modify cancer risk in LS families. This hypothesis was verified in the case of rs16892766 (8q23.3) and rs3802842 (11q23.1) in *MLH1* mutation carriers[6-8]. Similarly, we recently identified an association between the presence of a common variant in the telomerase gene (*hTERT* rs2075786) that causes shorter telomeres and an increased risk of developing LS-related tumors at a young age (< 45 years) in two independent series of patients with LS[56]. The identification of additional modifying factors will enable the estimation of individualized cancer risks that can be used to deliver tailored clinical surveillance protocols to mutation carriers.

Familial adenomatous polyposis

Familial adenomatous polyposis (FAP; MIM No. 175000) is the second most common inherited CRC syndrome. In its classic form, FAP is an autosomal dominantly inherited disease characterized by the development of hundreds to thousands of colorectal adenomatous polyps after the first decade of life. FAP is estimated to have a prevalence of 2-3 per 100000 individuals and to account for 0.2%-1% of all CRCs[57-60]. If left untreated, the classic form of FAP results in nearly complete penetrance of CRC by the age of 50 years. FAP is usually classified into classic and attenuated FAP (AFAP) depending on the number of polyps detected. A summary of the clinical characteristics of FAP is shown in Table 3[61,62].

Most classic FAP cases arise as a consequence of a germline heterozygous mutation in adenomatous polyposis coli (APC), a gene located on chromosome 5q21. All individuals who carry a germline pathogenic mutation in the *APC* gene (the first hit according to Knudson's two-hit hypothesis) eventually develop FAP. As is the case for other tumor suppressor genes, tumor development requires the somatic inactivation of the wild-type allele. Given that thousands of adenomas can form within 15-40 years, it is likely that only two hits are necessary for the initiation of tumorigenesis; however, given that only one or a few of these adenomas progress to cancer, it is likely that several additional mutations are needed[63,64].

In most cases of FAP, the *APC* mutation is inherited in an autosomal dominant manner; however, in 15%-20% of cases, the *APC* mutation appears to arise *de novo* (*i.e.*, spontaneously). Patients with these types of mutations therefore do not present with a family history of the disease[65]. However, approximately 20% of individuals with an apparent *de novo APC* mutation appear to have somatic mosaicism[66].

A truncating germline *APC* mutation that constitutively activates the Wnt pathway can be detected in approximately 80% of classic FAP cases[67-69], whereas fewer than 30% of individuals with attenuated phenotypes carry an identifiable *APC* mutation[70]. Approximately 90% of mutations are detected by sequence analysis (small intragenic deletions/insertions and missense, nonsense

Table 4 Clinical characteristics of individuals with suspected *MUTYH*-associated polyposis

Clinical characteristics
One to ten colonic adenomas before 40 yr of age
Tens to hundreds of colonic adenomas and/or hyperplastic polyps
Colonic polyposis (*i.e.*, > 100 colonic polyps) in the absence of a germline *APC* mutation
Colorectal cancer with the somatic *KRAS* mutation c.34G>T in codon 12
Family history of colon cancer (with or without polyps) consistent with autosomal recessive inheritance

The definitive diagnosis is confirmed by the presence of a biallelic *MUTYH* mutation. APC: Adenomatous polyposis coli.

or splice-site mutations); the remaining 8%-12% consist of whole or partial gene deletions[67-69,71,72]. Moreover, interstitial deletions of chromosome 5q22 that also delete *APC* have been reported in individuals with the classic and attenuated forms of FAP. These individuals often have dysmorphic features and mild-to-moderate cognitive impairments[73,74]. No germline epimutations (CpG island methylation) have been identified in the *APC* gene[75].

It is widely accepted that the methods used to identify mutations fail to detect certain mutations because of factors such as polymorphisms in the sequences to which PCR primers bind that lead to allele dropout, or due to somatic mosaicism or because the mutations occur in regions not targeted by the currently used methods. Castellsagué *et al*[76] and Spier *et al*[77] reported the occurrence of imbalanced allele-specific expression of *APC* in 8%-9% of *APC*/*MUTYH* mutation-negative polyposis cases, indicating that the underlying mutations were not detected by standard mutation detection techniques. Some of these cases carried pathogenic deep intronic variants predicted to activate cryptic splice sites[77], whereas others carried mutations in the promoter region of *APC*[78].

If no disease-causing *APC* mutation is found, molecular genetic testing of *MUTYH*, *POLE* and *POLD1* (exons coding for the exonuclease domain) should be considered (more information on *MUTYH*- and polymerase proofreading-associated polyposes can be found in the corresponding sections of this review).

In FAP, mutations in certain codons or regions are associated with specific phenotypic features. For example, profuse polyposis (which corresponds to an average of 5000 polyps) has been reported to be associated with mutations in codons 1250-1464[79]; AFAP is associated with mutations in the 5' region of the gene (codons 1-177), in exon 9 and in the 3' region of the gene[80-84]. AFAP has also been associated with interstitial deletions of chromosome 5q22 that also delete *APC*[73] and with somatic mosaicism for *APC* mutations that are generally associated with classic FAP[66,85,86]. *APC* mutations that cause Gardner's syndrome typically occur in the region between codons 1403 and 1578. Additionally, certain genotypes have been found to be associated with extracolonic manifestations of the disease[87].

MUTYH-associated polyposis

Bi-allelic (homozygous or compound heterozygous) mutations in the *MUTYH* gene, which encodes a base excision repair protein, are responsible for certain cases of adenomatous polyposis. *MUTYH*-associated-polyposis (MAP; MIM No. 608456) represents the first known polyposis syndrome with a recessive pattern of inheritance; therefore, the disease is theoretically restricted to one generation.

Because of the variability in clinical features observed among mutation carriers, the diagnosis of MAP based on clinical findings alone remains difficult. Two thirds of MAP patients have CRC at the time of diagnosis, and up to one third of patients have CRC but no polyps. Most MAP patients have < 100 adenomas at diagnosis and a mean age of 45 years; these patients tend to develop CRC at a mean age of 50 years[88-92]. Other features variably present in MAP include: duodenal polyps and cancer; gastric fundic gland polyps; gastric, ovarian, bladder, breast or endometrial tumors; benign and malignant tumors of the skin and thyroid gland; dental abnormalities (jaw-bone cysts); and CHPRE[93-97]. Because the phenotypes associated with MAP are highly variable, a wide spectrum of clinical characteristics should be considered in patients with suspected MAP (Table 4)[98,99].

The MUTYH protein is a base excision repair glycosylase involved in repairing one of the most frequent and stable forms of oxidative damage, namely the oxidation of a guanine leading to the formation of 8-oxo-7, 8-dihydro-2'-deoxyguanosine (8-oxoG). When an oxoG: A mismatch is present in the DNA-template, a G:C to T: A transversion occurs in the subsequent round of replication[100]. For this reason, G:C to T:A transversions frequently occur in *MUTYH*-associated adenomas and tumors. One such transversion in the *KRAS* gene (c.34G>T in codon 12) is frequently encountered (64%) in patients with MAP CRC. Therefore, the analysis of somatic *KRAS* has been recommended as a pre-screening test to identify CRC patients eligible for *MUTYH* germline molecular genetic testing[98,101,102].

Colorectal tumors that develop in the context of a *MUTYH* mutation have specific molecular and histological features that differentiate these tumors from sporadic tumors and that overlap with features of hereditary (LS) and sporadic MSI tumors. These features include a preferential proximal location, a mucinous component and the increased presence of tumor infiltrating lymphocytes. However, only a minority (range: 0%-18%) of *MUTYH*-associated tumors exhibit MSI. All of these features raise the suspicion of a MAP etiology for the CRC, especially when the disease is diagnosed at a young age and when polyps and/or a recessive inheritance pattern are detected[103].

Approximately 30% of *APC* mutation-negative cases of polyposis harbor bi-allelic mutations in the *MUTYH* gene. At least one of two *MUTYH* missense mutations found in 1%-2% of the general population [c.536A>G (p.Tyr179Cys) and c.1187G>A (p.Gly396Asp), annotated

according to the longest (hypothetical) coding sequence NM 001128425.1] is present in approximately 90% of MAP patients in the western part of the world; a biallelic status for one and/or the other variant was found in up to 70% of Caucasian patients with MAP[98]. Additional common mutations that were most likely founder mutations have been reported in different populations: the c.1147delC (p.Ala385Profs*23) mutation was reported in northern European MAP patients, the c.1214C>T (p.Pro405Leu) mutation was reported in Dutch MAP patients, the c.1437_1439del (p.Glu480del) mutation was reported in Italian MAP patients, the c.1438G>T (p.Glu480*) mutation was reported in British Indian MAP patients, the p.Tyr104* mutation was reported in Pakistani MAP patients, the c.1227_1228dup (p.Glu410Glyfs*43) mutation was reported in Spanish, Portuguese and Tunisian MAP patients and the p.Ala359Val mutation was reported in Japanese and Korean MAP patients[90,104-111]. The presence of recurrent mutations facilitates genetic testing for *MUTYH*, thus allowing for an initial screening of the common mutations found in the corresponding population.

Polymerase proofreading-associated polyposis

DNA polymerase ε (*POLE*) and δ (*POLD1*) mutations have recently been identified in patients with familial CRC, many of whom have multiple adenomas[112].

The two germline mutations *POLE* p.Leu424Val and *POLD1* p.Ser478Asn were detected in individuals with multiple colorectal adenomas and CRC. An additional variant of *POLD1*, p.Pro327Leu, the pathogenicity of which has not yet been determined, was also identified in a multiple adenoma patient[112]. 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 an increased risk of endometrial cancer in female carriers[112,113]. A recent study performed by our group identified a *de novo POLE* p.L424V mutation in patient with adenomatous polyposis and early onset CRC, and a novel pathogenic mutation in *POLD1*, p.L474P, in a non-polyposis Amsterdam Ⅱ family without MMR defects[113]. Based on these findings, the term "polymerase proofreading-associated polyposis" may be misleading and should be carefully used, at least until more *POLE*/*POLD1* families are described and the full phenotypic spectrum of this syndrome is defined.

All germline mutations identified thus far in *POLE* and *POLD1* are located within the proofreading (exonuclease) domain of the respective polymerase, suggesting a deficient ability to proofread and repair errors during DNA replication[112,114-116]. Non-exonuclease domain *POLE* and *POLD1* mutations do not appear to be associated with familial CRC. Mutations in non-exonuclease domain regions have been identified in colorectal and endometrial tumors that are mostly MSI-positive; however, these mutations appear to be passenger mutations[116].

Tumors that develop in patients with polymerase proofreading-associated polyposis and sporadic colorectal and endometrial tumors with *POLE* mutations (somatic *POLD1* mutations are rare) are hypermutant and microsatellite-stable. These hypermutated tumors have approximately 5000 somatic base substitutions in their coding regions and an altered mutation spectrum characterized mostly by increased proportions of G:C→T:A and A:T →C:G transversions[116]. As is the case with microsatellite instability in LS, a feasible molecular approach for identifying hypermutated tumors in patients with polyposis should be developed to facilitate the selection of cases suspected of carrying germline polymerase proofreading mutations.

Although the phenotypes associated with *POLE* and *POLD1* mutations vary among carriers, the evidence gathered so far supports the recommendation of the sequencing of the exonuclease domains of *POLE* and *POLD1* for genetic testing purposes.

Hereditary mixed polyposis syndrome

Hereditary mixed polyposis syndrome (HMPS; MIM No. 601228) is an unusual disease characterized by the apparent autosomal dominant inheritance of multiple types of colorectal lesions (including Peutz-Jeghers polyps, juvenile polyps, serrated lesions, conventional adenomas and CRC) and a lack of extracolonic manifestations[117].

Linkage studies conducted in large families identified *CRAC1* on chromosome 15q13.3 as the candidate region that causes HMPS[118,119]. Moreover, families of Ashkenazi descent with hereditary mixed polyposis syndrome shared a disease haplotype in the *CRAC1* region[120]. The sequencing of the shared region did not yield useful results; however, the study of copy number alterations revealed the presence of a heterozygous single-copy duplication of a region approximately 40 kb in length that co-segregated with the disease. The duplication extended from intron 2 of *SCG5* to a site immediately upstream of the *GREM1* CpG island. The *SCG5-GREM1* duplication increased the transcription of *GREM1*, a gene that encodes the secreted BMP antagonist[121]. No non-Ashkenazi affected individuals with duplications in the region implicated in HMPS have yet been identified.

Hamartomatous polyposis syndromes

Juvenile polyposis: Juvenile polyposis syndrome (JPS; MIM No. 174900) is the most common hamartomatous syndrome, with an estimated incidence of one per 100000[122].

The diagnosis of JPS is made when any of the following three criteria is met[123-125]: (1) the patient has multiple (3-10) juvenile polyps of the colorectum; (2) a patient with a familial history of JPS has any number of juvenile polyps; or (3) the patient has extracolonic (*e.g.*, in the stomach or small intestine) juvenile polyps.

Juvenile polyps are hamartomas that have a normal epithelium with a dense stroma, an inflammatory infiltrate and a smooth surface with dilated, mucus-filled

cystic glands in the lamina propria. Most juvenile polyps are benign; however, malignant transformation can occur. Members of families with JPS have an estimated lifetime risk of developing gastrointestinal cancer of 9% to 50%[126]. Most of these cancers consist of colon cancer; however, cancers of the stomach, upper gastrointestinal tract and pancreas have also been reported[122].

Germline mutations in *SMAD4* or in *BMPR1A* have been identified in approximately 40% of JPS patients[127,128]. Both genes encode proteins involved in the TGF-beta signaling pathway, an important modulator of many cellular processes.

JPS patients with mutations in the *SMAD4* gene are predisposed to developing massive gastric polyps and usually have a family history of upper gastrointestinal polyposis[127,129]. A large proportion of JPS patients with *SMAD4* mutations have a juvenile polyposis/hereditary hemorrhagic telangiectasia overlap syndrome (MIM No. 175050). Hereditary hemorrhagic telangiectasia is a dominant disorder characterized by epistaxis, visceral arteriovenous malformations and telangiectasias[130].

Sweet *et al*[131] found two rare germline variants of *ENG*, a gene associated with a predisposition to hereditary hemorrhagic telangiectasia, in two JPS patients with no symptoms of hemorrhagic telangiectasia. Subsequent studies in other JPS patients did not identify deleterious *ENG* mutations in genetically uncharacterized JPS patients[132-134]. *PTEN* mutations have been identified in JPS patients[134]; however, it has been suggested that these patients were clinically misclassified and most likely belonged to the *PTEN* hamartoma tumor group[135]. Microdeletions at 10q22-q23, a region that includes both *PTEN* and *BMPR1A,* have also been reported[136].

Peutz-Jeghers syndrome: Peutz-Jeghers syndrome (PJS; MIM No. 175200) is an autosomal-dominant condition caused by germline mutations in *STK11* (formerly known as *LKB1)*, which encodes a serine-threonine kinase. PJS is clinically characterized by the occurrence of gastrointestinal polyposis and mucocutaneous pigmentation and a predisposition to develop cancer.

The presence of PJS-type hamartomatous intestinal polyps is required for a clinical diagnosis of PJS, even though these patients also develop other types of polyps, including colonic adenomatous polyps or gastric PJS polyps that resemble hyperplastic polyps. PJS-type polyps have characteristic histological features, including a notable frond-like, elongated epithelial component, cystic gland dilatation extending into the submucosa or muscularis propria and arborizing smooth muscle extending into the polyp fronds. These polyps are found throughout the gastrointestinal tract but occur predominantly in the small intestine and colon[137].

Cutaneous lesions found in patients with PJS include small melanocytic macules on the labial mucosa, lips, palate and tongue, around the eyes and nostrils and in the perianal region. Hyperpigmented macules on the fingers are also common. Mucocutaneous pigmented lesions, which usually develop in childhood, are found in 95% of patients with PJS[138,139].

A clinical diagnosis can be made when any of the following criteria are fulfilled[137]: (1) the patient has two or more histologically confirmed PJS-type hamartomatous polyps; (2) a patient with a family history of PJS has any number of PJS-type polyps; (3) a patient with a family history of PJS has characteristic mucocutaneous pigmentation; (4) a patient with characteristic mucocutaneous pigmentation has any number of PJS-type polyps; and (5) the patient has a pathogenic mutation in *STK11*.

The risk of gastrointestinal and extraintestinal malignancies, including duodenal, colon, breast, pancreas, stomach, small bowel, cervix, uterus, ovary, testes, and thyroid tumors, is significantly increased in patients with JPS[140-143]. Benign and malignant gonadal and gynecologic tumors, including ovarian sex cord tumors with annular tubules, mucinous tumors of the ovaries and fallopian tubes and large-cell calcifying Sertoli cell tumors of the testes, can also be observed in these patients[144].

The clinical manifestations of JPS can vary; however, there are no reports of *STK11* mutation carriers lacking clinical manifestations of the disease.

Aretz *et al*[145] reported that 100% of individuals with familial PJS have detectable *STK11* mutations, whereas 91% of simplex cases (*i.e.*, a single occurrence in a family) who met the relevant diagnostic criteria had a detectable mutation. Clinical misdiagnoses of PJS could account for the decreased rate of detection of mutations in simplex cases.

***PTEN* hamartoma tumor syndrome:** The *PTEN* hamartoma tumor syndrome (PHTS, MIM No. 601728) comprises Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome, *PTEN*-related Proteus syndrome and Proteus-like syndrome. A presumptive diagnosis of PHTS is based on clinical signs; the definitive diagnosis of PHTS is, by definition, made only when a *PTEN* mutation is identified. The clinical characteristics of PHTS are shown in Table 5[146]. The specific clinical features of the four PHTS syndromes were reviewed by Orloff and Eng[147] and are not further described in this review.

The clinical phenotypes of *PTEN* mutation carriers are highly variable and range from macrocephaly and developmental delays (reported in a two-year-old patient) to a history of multiple primary neoplasias (reported in a 60-year-old patient)[146]. However, to date, no strong genotype-phenotype correlations have been reported[148]. Moreover, significant intra-familial phenotypic variability and overlapping mutation spectra have been observed[149].

The lifetime risks for a variety of cancers are increased in patients with PHTS; more specifically, these patients have an estimated lifetime risk of breast, thyroid, endometrial, renal cell and colon tumors and melanoma of 85%, 35%, 28% 34%, 9% and 6%, respectively[150,151].

Germline *PTEN* mutations have been identified in patients with autism/ pervasive developmental disorder and macrocephaly and to a particularly significant extent

Table 5 Clinical characteristics of the *PTEN* hamartoma tumor syndrome

Clinical characteristics
Benign neoplasia
Dermatologic
Palmoplantar keratoses
Trichilemmomas
Lipomas
Fibromas
Freckling of the glans penis
Vascular anomalies/hemangiomas
Lhermitte-Duclos (dysplastic gangliocytoma of the cerebellum)
Genitourinary tumors/malformations
Colorectal polyposis
Mucosal lesions
Thyroid goiter/nodules
Proliferative breast changes
Malignant neoplasia
Breast cancer
Non-medullary thyroid cancer
Renal cancer
Endometrial cancer
Colorectal cancer
Melanoma
Central nervous system
Macrocephaly
Autism/developmental delay
Dysmorphic characteristics
Dolichocephaly
Postaxial polydactyly

in patients with a personal or family history of Cowden or Bannayan-Riley-Ruvalcaba syndromes[152-156].

To determine whether germline methylation is found in patients with Cowden syndrome and in patients with a Cowden-like syndrome who lack germline PTEN mutations, Bennett *et al*[157] observed that germline methylation upstream of PTEN occurred in 42% and 33% of mutation-negative patients with Cowden syndrome and Cowden-like syndromes, respectively. This hypermethylation did not silence *PTEN*. However, a newly characterized tumor suppressor gene, *KILLIN*, the promoter of which overlaps with the *PTEN* 5'UTR and the 5' end of its coding region, was silenced by this hypermethylation. This finding must be validated in other groups of patients before it can be used for diagnostic purposes.

Current challenges and future perspectives in genetically characterized inherited syndromes

One of the most significant challenges for researchers, clinicians and genetic counselors in treating or investigating hereditary CRC (and any other cancer syndrome) involves the assessment of the pathogenicity of variants of unknown or uncertain significance (VUS). Enormous efforts are currently being undertaken to establish gene-specific interpretation guidelines that can be made available to diagnostic laboratories, research laboratories, genetic counselors and clinicians worldwide. Some of these efforts have been conducted with the support and coordination of international societies or consortiums; for example, the International Society for Gastrointestinal Hereditary Tumors (InSiGHT), which is under the umbrella of the Human Variome Project, has attempted to classify *MMR* VUS (http://www.insight-group.org/variants/classifications/)[158].

When a pathogenic germline mutation is identified in a family, carriers of the mutation can benefit from increased surveillance and a more informed decision about preventive measures; at the same time, non-carriers do not have to undergo intensive (and, in the case of CRC, invasive) surveillance. In the absence of an identified pathogenic mutation, these individuals may decide to undergo preventive surgery based on family history alone. The effects of germline variants in many of the main cancer-related genes on protein function are unknown (VUS); as a result, it is difficult to make any inferences on the risk of cancer in patients with these variants. It has been estimated that up to 10% of Caucasians undergoing genetic testing have variants that are designated VUS, which leads to important issues in genetic counseling. Current attempts to classify these variants involve the use of data from co-segregation studies, *in silico* functional predictions, personal and family cancer history, the co-occurrence of these variants and pathogenic mutations, the frequency of these variants in the general population (controls), molecular characteristics of the tumors, effects on RNA (splicing, allele-specific expression) and *in vitro* functional consequences, which, in the case of *MMR* genes, include impairment of MMR activity and the abnormal subcellular localization and abrogation of the formation of physiological dimers[158-164].

The coupling of next-generation sequencing technologies with genomic sequence enrichment methods has made the sequencing of comprehensive panels of cancer-predisposing genes technically feasible; consequently, this approach has become cost-effective for diagnostic applications and can be used to overcome the issue of syndrome-overlapping genes and gene-overlapping syndromes. However, the more frequent use of this approach for genetic diagnostic purposes will result in an exponentially increased number of identified VUS and a more urgent need to classify these VUS to their highest level.

Another challenge for the coming years involves the identification of additional cancer risk modifiers, including environmental and genetic factors. Identifying these factors for syndromes with incomplete cancer penetrance will facilitate an accurate individual risk assessment that will enable the application of personalized surveillance protocols and preventive measures. For example, the importance of individual risk assessments is supported by the extreme heterogeneity in CRC risk in carriers of *MMR* gene mutations. Dowty *et al*[165] studied 17500 family members of 166 *MLH1*-mutated and 224 *MSH2*-mutated families and showed that the cumulative risk of CRC by age 70 follows a U-shaped distribution. These authors also observed that 17% of male *MSH2* mutation carriers have estimated lifetime risks of CRC of 0%-10% and that 18% of these carriers have lifetime risks of

Table 6 Genetic variants identified using candidate-gene association studies

Gene	Variant	Frequency in controls	OR (95%CI)	Cumulative evidence of association	Ethnicity
MUTYH	Biallelic mutation	0.01%	10.19 (5.0-22.0)	Strong	Caucasian
MUTYH	G382D (rs36053993)	0.00%	6.49 (2.6-10.4)	Strong	Caucasian
MUTYH	Y165C (rs34612342)	0.01%	3.32 (1.1-9.8)	Strong	Caucasian
APC	I1307K (rs1801155)	6.80%	1.96 (1.4-2.8)	Strong	Ashkenazi
CHEK2	1100delC	0.71%	1.88 (1.3-2.7)	Strong	Caucasian
CHEK2	I157T (rs17879961)	3.91%	1.56 (1.3-1.8)	Strong	Caucasian
MLH1	rs1800734 (promoter)	21.11%	1.51 (1.3-1.7)	Strong	Caucasian
DNMT3B	rs1569686 (promoter)	16.99%	0.57 (0.5-0.7)	Strong	All
GSTM1	Present/null	50.64%	1.10 (1.0-1.2)	Moderate	All
TERT	rs2736100 (intron 2)	49.34%	1.07 (1.0-1.1)	Moderate	Caucasian

Genetic variants identified using candidate-gene association studies, significantly associated with a risk of colorectal cancer in meta-analyses and showing strong and moderate cumulative evidence of association according to Venice criteria and false-positive report probability tests[189].

90%-100%. If carriers who are at low risk of developing CRC can be distinguished from patients who will definitely develop a tumor, subsequent cancer surveillance strategies could be applied accordingly.

The existence of genetic anticipation in cancer syndromes and the mechanisms that might explain this phenomenon have been studied and discussed for years. In LS, despite the numerous reports and clinical observations identifying anticipation in the age of cancer onset in successive generations, it is still unclear whether true genetic anticipation contributes to the early diagnosis of LS. More recently, methods that correct for random effects, that isolate the confounding effect of changes in secular trends, screening and medical practices and that adjust for changes in age-specific incidence across birth cohorts, appear to confirm the presence of this phenomenon in families with LS[166-168]. However, the molecular mechanism underlying this phenomenon has not yet been identified. Telomere shortening, the accumulation of mismatch repair slippage events in subsequent generations and environmental factors have been suggested as causative mechanisms of anticipation[169,170]. Our group recently ruled out telomere length attrition as the cause of anticipation in patients with LS[171]. Anticipation has also been observed in patients with hereditary non-polyposis CRC without MMR deficiency[172].

LOW-PENETRANCE LOCI IDENTIFIED BY GWAS IN HEREDITARY CRC

GWAS conducted since 2007 using samples from the general population and common genetic markers (SNPs) have successfully identified low-penetrance loci associated with CRC. To date, at least 21 independent loci have been conclusively associated with the risk of CRC in Caucasians ($P < 5.0 \times 10^{-8}$, and these associations were confirmed in independent case-control series) (source: http://www.genome.gov/gwastudies). These loci include 1q25 (*LAMC1*)[173], 1q41 (*DUSP10*)[174], 2q32.3 (*NABP1*)[173], 3q26.2(*MYNN*)[174], 5q21[175], 6p21.2 (*CDKN1A*)[176], 8q23.3 (*EIF3H*)[177], 8q24.21 (*c-MYC*)[173,177-181], 10p14[177], 11q13.4 (*POLD3*)[176], 11q23.1[180], 12p13.3 (*CCND2*)[173], 12q13.13 (*DIP2B*, *ATF1*)[174], 14q22.2 (*BMP4*)[182], 15q13.3[181], 16q22.1 (*CDH1*)[182], 18q21.1 (*SMAD7*)[173,183], 19q13.11 (*RHPN2*)[182], 20p12.3[182], 20q13.33 (*LAMA5*)[174] and Xp22.2 (*SHROOM2*)[176].

There is almost no evidence of interactive effects among these loci. However, the distribution of alleles associated with a risk of CRC follows a normal distribution in both cases and controls, with a shift towards higher numbers of these alleles in cases, which is consistent with a polygenic model of disease predisposition. It has been estimated that individuals carrying a large number of these alleles have an approximately threefold higher risk of developing CRC than those with a median number of these alleles[184]. Data suggest that only a small proportion (at most 10%) of the heritability associated with CRC can be explained by the identified loci[174,182,184-188].

OTHER RISK VARIANTS

In addition to the low-risk variants identified by GWAS, numerous genetic variants (> 3500 variants in > 1300 genes) that are associated with a low-moderate risk of CRC have been identified through candidate-gene approaches. The results from these candidate-gene association studies are usually inconsistent and difficult to interpret. In an effort to comprehensively evaluate candidate-gene association studies for CRC, Ma *et al*[189] recently performed meta-analyses for variants included in at least three independent datasets (267 variants in 150 genes) and used Venice criteria and false-positive report probability tests to assess the evidence for true associations. A total of 67 variants in 50 genes were found to be significantly associated with a risk of CRC. The cumulative epidemiological evidence for a risk of CRC was strong, moderate and weak in eight, two and 52 of the variants, respectively. Table 6 shows the 10 variants with strong and moderate evidence of association and their estimated risks. The authors of this study suggested that these variants may explain approximately 5% of the familial cancer risk in Caucasians.

Table 7 Clinical criteria established for the identification of serrated polyposis

Clinical criteria
At least five serrated polyps proximal to the sigmoid colon, two of which are larger than 10 mm in diameter
Any number of serrated polyps occurring proximally to the sigmoid colon in an individual who has a first-degree relative with serrated polyposis
More than 20 serrated polyps of any size distributed throughout the colon

Diagnosis is made when one of the criteria is fulfilled.

HEREDITARY CRC OF UNKNOWN ETIOLOGY

Despite recent developments in genotyping and sequencing technologies, the genetic etiology of several familial CRCs, including serrated polyposis (formerly known as "hyperplastic polyposis") and hereditary non-polyposis CRC without a MMR defect (also known as familial CRC type X) remains unknown.

Serrated polyposis

SP is a rare condition characterized by multiple and/or large serrated colonic polyps and an increased risk of CRC. The diagnosis of serrated polyposis is made based on established clinical criteria[190] (Table 7). Patients with SP most likely consist of a heterogeneous group of patients with a variety of SP phenotypes that are most likely caused by different genetic alterations[191]. At least three different subgroups have been described: (1) a right-sided phenotype with large sessile serrated adenomas associated with early-onset CRC characterized by the presence of a *BRAF* mutation; (2) a left-sided phenotype with large amounts of small polyps characterized by the presence of a *KRAS* mutation; and (3) a mixed phenotype with features of phenotypes 1 and 2[191,192]. Conventional colonic adenomas have been identified in up to 80% of individuals with SP and are more frequently present in CRC-affected individuals with SP[193,194].

Reported case series indicate that 25%-70% of SP patients had CRC at the time of diagnosis or during follow-up. Additionally, 10%-50% of SP patients had a family history of CRC[191,195-199]. In fact, studies have reported a fivefold increase in the risk of CRC and a 3.5-fold increase in the risk of pancreatic cancer in first-degree relatives of individuals with SP[194,199,200].

Serrated polyps are the precursors of CRC tumors developed through the serrated neoplasia pathway, which is characterized by *BRAF* mutations and the CpG island methylator phenotype with or without MSI depending on whether *MLH1* is methylated. Several subtypes of serrated polyps have been defined: hyperplastic polyps, sessile serrated adenomas and traditional serrated adenomas[201]. However, the majority of CRC tumors arising in patients with serrated polyps exhibit a diverse range of molecular profiles and generally do not harbor molecular hallmarks of tumors developed *via* the serrated pathway[202].

Although the genetic basis of SP is unknown, both recessive and dominant transmission patterns have been proposed[197,203,204]. Because serrated polyps were reported in individuals with biallelic mutations in *PTEN*, *BMPR1A*, *SMAD4* and *MUTYH* or with a duplication in the *GREM1* gene[205-208], Clendenning *et al*[209] hypothesized that these genes might be altered in individuals with SP and might account for some of the cases with this condition. However, no deleterious germline mutations were identified in a case series of 65 patients with SP.

It has been suggested that lifestyle factors such as smoking, obesity and diet, which have been associated with the presence of serrated polyps[210-212], could be responsible for SP or for the modification of the risk of disease in the presence of predisposing genetic mutations or risk variants.

If the cause of SP is genetic, current sequencing and genotyping technologies or methods that identify copy number alterations, structural variants or epigenetic modifications can be used to understand the etiology of this disease in the near future.

Familial CRC type X

Approximately 40% of the families meeting the Amsterdam criteria for a diagnosis of hereditary non-polyposis CRC lack evidence of heritable defects in the MMR system; more specifically, these patients have no germline mutations in the *MMR* genes, no tumor microsatellite instability and no loss of immunohistochemical staining of the MMR proteins. Because the genetic etiology of this disease is unknown, these families are said to have fCRC-X. As has been the case for other familial cancer syndromes, the identification of the genes associated with fCRC-X will facilitate the molecular diagnosis of the disease and the development of appropriate surveillance guidelines and clinical management protocols for these patients.

Familial CRC-X is clearly clinically different from Lynch syndrome; in particular, patients with familial CRC-X have a lower incidence of CRC and a lower risk of extracolonic tumors and tend to develop cancer at a later age[213-217]. Familial CRC-X tumors are characterized by the presence of microsatellite stability and chromosomal instability and the absence of high CpG methylator phenotypes; these characteristics overlap with some of the characteristics of sporadic MMR-proficient tumors. However, some molecular features specific to familial CRC-X tumors have been reported[218-221].

Significant but mostly unsuccessful efforts have been made to understand the genetic cause(s) of fCRC-X. Several dominant predisposition loci that have been mapped to different chromosomal regions such as 3q13.31-q27.1, 3q22, 4q21.1, 5q14-q22, 7q31, 8q13.2, 9q22.2-31.2, 10p15.3-p15.1, 12q24.32 and 13q22.1-13q31.3 have been identified using genome-wide linkage studies in families with CRC; however, no causal genes have yet been identified[222-230].

Despite the ability of whole-exome and whole-genome sequencing to uncover numerous new causal mutations and genes in Mendelian disorders, few such genes and mutations have been identified in hereditary cancer syndromes[112,231,232] and none have been identified in fCRC-X.

Current evidence indicates that families with fCRC-X constitute a very heterogeneous group. Because the Amsterdam criteria indicate that this disease is characterized by strong familial aggregation, it is likely that certain cases of fCRC-X are caused by high-penetrance mutations (*i.e.*, that have a monogenic component). If this is the case, reports on new hereditary CRC genes identified by whole-exome or whole-genome strategies will likely be published in the near future. However, because no such genes have yet been identified, it is likely that any genes identified in the future would explain only a small number of fCRC-X cases.

In contrast, candidate-gene approaches have identified several high-penetrance genes that might be involved in the etiology of uncharacterized familial CRC[233-237].

It is likely that most of the familial aggregation observed in fCRC-X is associated with non-genetic factors. Lifestyle and environmental factors could interact with multiple genetic risk factors to increase the risk of CRC in these families. This scenario is consistent with a multifactorial disease model associated with polygenic diseases and supported by the less aggressive clinical characteristics of fCRC-X (*e.g.*, the late onset of the disease, the lower risk of CRC and the almost complete absence of multiple primary tumors).

Because some families appear to fit the monogenic model and others the polygenic model, finding the optimal approach for exploring the genetic basis of fCRC-X remains challenging[238]. The selection criteria used to identify patients with fCRC-X will need to include the Amsterdam criteria, a very early onset of cancer and severe clinical manifestations; these criteria and insightful data analyses will play a key role in determining the ability of exome sequencing to identify rare and deleterious mutations within gene-coding regions. Furthermore, it is possible that other mechanisms of gene silencing such as germline epigenetic or copy number alterations or the deregulation of tumor suppressor genes *via* regulatory non-coding RNAs such as microRNAs could be associated with the hereditary forms of the disease.

Elucidating the polygenic component of the disease will also remain challenging. GWAS of patients with fCRC-X would be very useful; however, collecting an adequate number of samples (thousands of samples) is almost impossible given the rarity of fCRC-X, even if samples were to be collected worldwide. A closely related approach based on the hypothesis that variants associated with the risk of CRC in the general population are also associated with the risk of CRC in fCRC-X involves genotyping the population-based GWAS CRC risk variants in a large fCRC-X cohort. GWAS have already provided evidence suggesting that low-penetrance alleles may explain the risk of cancer in familial cases[187,188,239]. Sequencing the loci identified by GWAS to identify common and rare variants in patients with fCRC-X therefore represents an alternative approach. This approach has been successfully used in other diseases such as hypertriglyceridemia, diabetes and inflammatory bowel disease[240-243].

In summary, the genetic basis of fCRC-X will become clearer when all of the approaches mentioned above are applied in practice. However, alternative mechanisms involving gene-gene and gene-environment interactions, epigenetic and structural alterations and other non-classic gene silencing mechanisms might explain fCRC-X cases that are not detected by current risk variant or mutation-identification techniques.

ACKNOWLEDGMENTS

I thank Marta Pineda for critical review of the paper.

REFERENCES

1 **Ferlay J**, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer* 2010; **127**: 2893-2917 [PMID: 21351269 DOI: 10.1002/ijc.25516]

2 **Lichtenstein P**, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, Pukkala E, Skytthe A, Hemminki K. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med* 2000; **343**: 78-85 [PMID: 10891514 DOI: 10.1056/NEJM200007133430201]

3 **Aaltonen L**, Johns L, Järvinen H, Mecklin JP, Houlston R. Explaining the familial colorectal cancer risk associated with mismatch repair (MMR)-deficient and MMR-stable tumors. *Clin Cancer Res* 2007; **13**: 356-361 [PMID: 17200375 DOI: 10.1158/1078-0432.CCR-06-1256]

4 **Abdel-Rahman WM**, Peltomäki P. Lynch syndrome and related familial colorectal cancers. *Crit Rev Oncog* 2008; **14**: 1-22; discussion 23-31 [PMID: 19105568 DOI: 10.1615/CritRevOncog.v14.i1.10]

5 **Theodoratou E**, Montazeri Z, Hawken S, Allum GC, Gong J, Tait V, Kirac I, Tazari M, Farrington SM, Demarsh A, Zgaga L, Landry D, Benson HE, Read SH, Rudan I, Tenesa A, Dunlop MG, Campbell H, Little J. Systematic meta-analyses and field synopsis of genetic association studies in colorectal cancer. *J Natl Cancer Inst* 2012; **104**: 1433-1457 [PMID: 23019048 DOI: 10.1093/jnci/djs369]

6 **Wijnen JT**, Brohet RM, van Eijk R, Jagmohan-Changur S, Middeldorp A, Tops CM, van Puijenbroek M, Ausems MG, Gómez García E, Hes FJ, Hoogerbrugge N, Menko FH, van Os TA, Sijmons RH, Verhoef S, Wagner A, Nagengast FM, Kleibeuker JH, Devilee P, Morreau H, Goldgar D, Tomlinson IP, Houlston RS, van Wezel T, Vasen HF. Chromosome 8q23.3 and 11q23.1 variants modify colorectal cancer risk in Lynch syndrome. *Gastroenterology* 2009; **136**: 131-137 [PMID: 19010329 DOI: 10.1053/j.gastro.2008.09.033]

7 **Talseth-Palmer BA**, Brenne IS, Ashton KA, Evans TJ, McPhillips M, Groombridge C, Suchy J, Kurzawski G, Spigelman A, Lubinski J, Scott RJ. Colorectal cancer susceptibility loci on chromosome 8q23.3 and 11q23.1 as modifiers for disease expression in Lynch syndrome. *J Med Genet* 2011; **48**: 279-284 [PMID: 21097774 DOI: 10.1136/jmg.2010.079962]

8 **Talseth-Palmer BA**, Wijnen JT, Grice DM, Scott RJ. Genetic modifiers of cancer risk in Lynch syndrome: a review. *Fam Cancer* 2013; **12**: 207-216 [PMID: 23471748 DOI: 10.1007/s10689-013-9614-2]

9 **Lynch HT**, Lynch PM, Lanspa SJ, Snyder CL, Lynch JF, Boland CR. Review of the Lynch syndrome: history, molecular genetics, screening, differential diagnosis, and medicolegal ramifications. *Clin Genet* 2009; **76**: 1-18 [PMID: 19659756 DOI: 10.1111/j.1399-0004.2009.01230.x]

10 **Wimmer K**, Kratz CP. Constitutional mismatch repair-deficiency syndrome. *Haematologica* 2010; **95**: 699-701 [PMID: 20442441 DOI: 10.3324/haematol.2009.021626]

11 **Hemminki A**, Peltomäki P, Mecklin JP, Järvinen H, Salovaara R, Nyström-Lahti M, de la Chapelle A, Aaltonen LA. Loss of the wild type MLH1 gene is a feature of hereditary nonpolyposis colorectal cancer. *Nat Genet* 1994; **8**: 405-410 [PMID: 7894494 DOI: 10.1038/ng1294-405]

12 **Liu B**, Parsons RE, Hamilton SR, Petersen GM, Lynch HT, Watson P, Markowitz S, Willson JK, Green J, de la Chapelle A. hMSH2 mutations in hereditary nonpolyposis colorectal cancer kindreds. *Cancer Res* 1994; **54**: 4590-4594 [PMID: 8062247]

13 **Liu B**, Nicolaides NC, Markowitz S, Willson JK, Parsons RE, Jen J, Papadopolous N, Peltomäki P, de la Chapelle A, Hamilton SR. Mismatch repair gene defects in sporadic colorectal cancers with microsatellite instability. *Nat Genet* 1995; **9**: 48-55 [PMID: 7704024 DOI: 10.1038/ng0195-48]

14 **Kane MF**, Loda M, Gaida GM, Lipman J, Mishra R, Goldman H, Jessup JM, Kolodner R. Methylation of the hMLH1 promoter correlates with lack of expression of hMLH1 in sporadic colon tumors and mismatch repair-defective human tumor cell lines. *Cancer Res* 1997; **57**: 808-811 [PMID: 9041175]

15 **Aaltonen LA**, Peltomäki P, Leach FS, Sistonen P, Pylkkänen L, Mecklin JP, Järvinen H, Powell SM, Jen J, Hamilton SR. Clues to the pathogenesis of familial colorectal cancer. *Science* 1993; **260**: 812-816 [PMID: 8484121 DOI: 10.1126/science.8484121]

16 **Aaltonen LA**, Peltomäki P, Mecklin JP, Järvinen H, Jass JR, Green JS, Lynch HT, Watson P, Tallqvist G, Juhola M. Replication errors in benign and malignant tumors from hereditary nonpolyposis colorectal cancer patients. *Cancer Res* 1994; **54**: 1645-1648 [PMID: 8137274]

17 **Palomaki GE**, McClain MR, Melillo S, Hampel HL, Thibodeau SN. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genet Med* 2009; **11**: 42-65 [PMID: 19125127 DOI: 10.1097/GIM.0b013e31818fa2db]

18 **Stupart DA**, Goldberg PA, Algar U, Ramesar R. Surveillance colonoscopy improves survival in a cohort of subjects with a single mismatch repair gene mutation. *Colorectal Dis* 2009; **11**: 126-130 [PMID: 19143775 DOI: 10.1111/j.1463-1318.2008.01702.x]

19 **Vasen HF**, Mecklin JP, Khan PM, Lynch HT. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). *Dis Colon Rectum* 1991; **34**: 424-425 [PMID: 2022152 DOI: 10.1007/BF02053699]

20 **Park JG**, Vasen HF, Park KJ, Peltomaki P, Ponz de Leon M, Rodriguez-Bigas MA, Lubinski J, Beck NE, Bisgaard ML, Miyaki M, Wijnen JT, Baba S, Lynch HT. Suspected hereditary nonpolyposis colorectal cancer: International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC) criteria and results of genetic diagnosis. *Dis Colon Rectum* 1999; **42**: 710-715; discussion 715-716 [PMID: 10378593 DOI: 10.1007/BF02236922]

21 **Hampel H**, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, Nakagawa H, Sotamaa K, Prior TW, Westman J, Panescu J, Fix D, Lockman J, Comeras I, de la Chapelle A. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). *N Engl J Med* 2005; **352**: 1851-1860 [PMID: 15872200 DOI: 10.1056/NEJMoa043146]

22 **Sjursen W**, Haukanes BI, Grindedal EM, Aarset H, Stormorken A, Engebretsen LF, Jonsrud C, Bjørnevoll I, Andresen PA, Ariansen S, Lavik LA, Gilde B, Bowitz-Lothe IM, Maehle L, Møller P. Current clinical criteria for Lynch syndrome are not sensitive enough to identify MSH6 mutation carriers. *J Med Genet* 2010; **47**: 579-585 [PMID: 20587412 DOI: 10.1136/jmg.2010.077677]

23 **Umar A**, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Rüschoff J, Fishel R, Lindor NM, Burgart LJ, Hamelin R, Hamilton SR, Hiatt RA, Jass J, Lindblom A, Lynch HT, Peltomaki P, Ramsey SD, Rodriguez-Bigas MA, Vasen HF, Hawk ET, Barrett JC, Freedman AN, Srivastava S. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 2004; **96**: 261-268 [PMID: 14970275 DOI: 10.1093/jnci/djh034]

24 **Laghi L**, Bianchi P, Roncalli M, Malesci A. Re: Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. *J Natl Cancer Inst* 2004; **96**: 1402-143; author reply 1402-1403 [PMID: 15367575 DOI: 10.1093/jnci/djh280]

25 **Samowitz WS**, Curtin K, Ma KN, Schaffer D, Coleman LW, Leppert M, Slattery ML. Microsatellite instability in sporadic colon cancer is associated with an improved prognosis at the population level. *Cancer Epidemiol Biomarkers Prev* 2001; **10**: 917-923 [PMID: 11535541]

26 **Hutchins G**, Southward K, Handley K, Magill L, Beaumont C, Stahlschmidt J, Richman S, Chambers P, Seymour M, Kerr D, Gray R, Quirke P. Value of mismatch repair, KRAS, and BRAF mutations in predicting recurrence and benefits from chemotherapy in colorectal cancer. *J Clin Oncol* 2011; **29**: 1261-1270 [PMID: 21383284 DOI: 10.1200/JCO.2010.30.1366]

27 **Pérez-Carbonell L**, Ruiz-Ponte C, Guarinos C, Alenda C, Payá A, Brea A, Egoavil CM, Castillejo A, Barberá VM, Bessa X, Xicola RM, Rodríguez-Soler M, Sánchez-Fortún C, Acame N, Castellví-Bel S, Piñol V, Balaguer F, Bujanda L, De-Castro ML, Llor X, Andreu M, Carracedo A, Soto JL, Castells A, Jover R. Comparison between universal molecular screening for Lynch syndrome and revised Bethesda guidelines in a large population-based cohort of patients with colorectal cancer. *Gut* 2012; **61**: 865-872 [PMID: 21868491 DOI: 10.1136/gutjnl-2011-300041]

28 **Sinicrope FA**, Foster NR, Thibodeau SN, Marsoni S, Monges G, Labianca R, Kim GP, Yothers G, Allegra C, Moore MJ, Gallinger S, Sargent DJ. DNA mismatch repair status and colon cancer recurrence and survival in clinical trials of 5-fluorouracil-based adjuvant therapy. *J Natl Cancer Inst* 2011; **103**: 863-875 [PMID: 21597022 DOI: 10.1093/jnci/djr153]

29 **Parsons MT**, Buchanan DD, Thompson B, Young JP, Spurdle AB. Correlation of tumour BRAF mutations and MLH1 methylation with germline mismatch repair (MMR) gene mutation status: a literature review assessing utility of tumour features for MMR variant classification. *J Med Genet* 2012; **49**: 151-157 [PMID: 22368298 DOI: 10.1136/jmedgenet-2011-100714]

30 **Manolio TA**. Bringing genome-wide association findings into clinical use. *Nat Rev Genet* 2013; **14**: 549-558 [PMID: 23835440 DOI: 10.1038/nrg3523]

31 **Hampel H**, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, Clendenning M, Sotamaa K, Prior T, Westman JA, Panescu J, Fix D, Lockman J, LaJeunesse J, Comeras I, de la Chapelle A. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. *J Clin Oncol* 2008; **26**: 5783-5788 [PMID: 18809606 DOI: 10.1200/JCO.2008.17.5950]

32 **de la Chapelle A**, Palomaki G, Hampel H. Identifying Lynch syndrome. *Int J Cancer* 2009; **125**: 1492-1493 [PMID: 19536819 DOI: 10.1002/ijc.24491]

33 **Heald B**, Plesec T, Liu X, Pai R, Patil D, Moline J, Sharp RR, Burke CA, Kalady MF, Church J, Eng C. Implementation of universal microsatellite instability and immunohistochemistry screening for diagnosing lynch syndrome in a large academic medical center. *J Clin Oncol* 2013; **31**: 1336-1340 [PMID: 23401454 DOI: 10.1200/JCO.2012.45.1674]

34 **Ward RL**, Hicks S, Hawkins NJ. Population-based molecular

screening for Lynch syndrome: implications for personalized medicine. *J Clin Oncol* 2013; **31**: 2554-2562 [PMID: 23733757 DOI: 10.1200/JCO.2012.46.8454]

35 **Teutsch SM**, Bradley LA, Palomaki GE, Haddow JE, Piper M, Calonge N, Dotson WD, Douglas MP, Berg AO. The Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Initiative: methods of the EGAPP Working Group. *Genet Med* 2009; **11**: 3-14 [PMID: 18813139 DOI: 10.1097/GIM.0b013e318184137c]

36 **Bellcross CA**, Bedrosian SR, Daniels E, Duquette D, Hampel H, Jasperson K, Joseph DA, Kaye C, Lubin I, Meyer LJ, Reyes M, Scheuner MT, Schully SD, Senter L, Stewart SL, St Pierre J, Westman J, Wise P, Yang VW, Khoury MJ. Implementing screening for Lynch syndrome among patients with newly diagnosed colorectal cancer: summary of a public health/clinical collaborative meeting. *Genet Med* 2012; **14**: 152-162 [PMID: 22237445 DOI: 10.1038/gim.0b013e31823375ea]

37 **Miyaki M**, Konishi M, Tanaka K, Kikuchi-Yanoshita R, Muraoka M, Yasuno M, Igari T, Koike M, Chiba M, Mori T. Germline mutation of MSH6 as the cause of hereditary nonpolyposis colorectal cancer. *Nat Genet* 1997; **17**: 271-272 [PMID: 9354786 DOI: 10.1038/ng1197-271]

38 **Berends MJ**, Wu Y, Sijmons RH, Mensink RG, van der Sluis T, Hordijk-Hos JM, de Vries EG, Hollema H, Karrenbeld A, Buys CH, van der Zee AG, Hofstra RM, Kleibeuker JH. Molecular and clinical characteristics of MSH6 variants: an analysis of 25 index carriers of a germline variant. *Am J Hum Genet* 2002; **70**: 26-37 [PMID: 11709755 DOI: 10.1086/337944]

39 **Peltomäki P**. Role of DNA mismatch repair defects in the pathogenesis of human cancer. *J Clin Oncol* 2003; **21**: 1174-1179 [PMID: 12637487 DOI: 10.1200/JCO.2003.04.060]

40 **Senter L**, Clendenning M, Sotamaa K, Hampel H, Green J, Potter JD, Lindblom A, Lagerstedt K, Thibodeau SN, Lindor NM, Young J, Winship I, Dowty JG, White DM, Hopper JL, Baglietto L, Jenkins MA, de la Chapelle A. The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. *Gastroenterology* 2008; **135**: 419-428 [PMID: 18602922 DOI: 10.1053/j.gastro.2008.04.026]

41 **Niessen RC**, Hofstra RM, Westers H, Ligtenberg MJ, Kooi K, Jager PO, de Groote ML, Dijkhuizen T, Olderode-Berends MJ, Hollema H, Kleibeuker JH, Sijmons RH. Germline hypermethylation of MLH1 and EPCAM deletions are a frequent cause of Lynch syndrome. *Genes Chromosomes Cancer* 2009; **48**: 737-744 [PMID: 19455606 DOI: 10.1002/gcc.20678]

42 **Kuiper RP**, Vissers LE, Venkatachalam R, Bodmer D, Hoenselaar E, Goossens M, Haufe A, Kamping E, Niessen RC, Hogervorst FB, Gille JJ, Redeker B, Tops CM, van Gijn ME, van den Ouweland AM, Rahner N, Steinke V, Kahl P, Holinski-Feder E, Morak M, Kloor M, Stemmler S, Betz B, Hutter P, Bunyan DJ, Syngal S, Culver JO, Graham T, Chan TL, Nagtegaal ID, van Krieken JH, Schackert HK, Hoogerbrugge N, van Kessel AG, Ligtenberg MJ. Recurrence and variability of germline EPCAM deletions in Lynch syndrome. *Hum Mutat* 2011; **32**: 407-414 [PMID: 21309036 DOI: 10.1002/humu.21446]

43 **Valle L**, Carbonell P, Fernandez V, Dotor AM, Sanz M, Benitez J, Urioste M. MLH1 germline epimutations in selected patients with early-onset non-polyposis colorectal cancer. *Clin Genet* 2007; **71**: 232-237 [PMID: 17309645 DOI: 10.1111/j.1399-0004.2007.00751.x]

44 **Hitchins MP**. The role of epigenetics in Lynch syndrome. *Fam Cancer* 2013; **12**: 189-205 [PMID: 23462881 DOI: 10.1007/s10689-013-9613-3]

45 **Ward RL**, Dobbins T, Lindor NM, Rapkins RW, Hitchins MP. Identification of constitutional MLH1 epimutations and promoter variants in colorectal cancer patients from the Colon Cancer Family Registry. *Genet Med* 2013; **15**: 25-35 [PMID: 22878509 DOI: 10.1038/gim.2012.91]

46 **Wijnen J**, van der Klift H, Vasen H, Khan PM, Menko F, Tops C, Meijers Heijboer H, Lindhout D, Møller P, Fodde R. MSH2 genomic deletions are a frequent cause of HNPCC. *Nat Genet* 1998; **20**: 326-328 [PMID: 9843200 DOI: 10.1038/3795]

47 **Charbonnier F**, Raux G, Wang Q, Drouot N, Cordier F, Limacher JM, Saurin JC, Puisieux A, Olschwang S, Frebourg T. Detection of exon deletions and duplications of the mismatch repair genes in hereditary nonpolyposis colorectal cancer families using multiplex polymerase chain reaction of short fluorescent fragments. *Cancer Res* 2000; **60**: 2760-2763 [PMID: 10850409]

48 **Wagner A**, Barrows A, Wijnen JT, van der Klift H, Franken PF, Verkuijlen P, Nakagawa H, Geugien M, Jaghmohan-Changur S, Breukel C, Meijers-Heijboer H, Morreau H, van Puijenbroek M, Burn J, Coronel S, Kinarski Y, Okimoto R, Watson P, Lynch JF, de la Chapelle A, Lynch HT, Fodde R. Molecular analysis of hereditary nonpolyposis colorectal cancer in the United States: high mutation detection rate among clinically selected families and characterization of an American founder genomic deletion of the MSH2 gene. *Am J Hum Genet* 2003; **72**: 1088-1100 [PMID: 12658575 DOI: 10.1086/373963]

49 **Plaschke J**, Krüger S, Dietmaier W, Gebert J, Sutter C, Mangold E, Pagenstecher C, Holinski-Feder E, Schulmann K, Möslein G, Rüschoff J, Engel C, Evans G, Schackert HK. Eight novel MSH6 germline mutations in patients with familial and nonfamilial colorectal cancer selected by loss of protein expression in tumor tissue. *Hum Mutat* 2004; **23**: 285 [PMID: 14974087 DOI: 10.1002/humu.9217]

50 **Pineda M**, González S, Lázaro C, Blanco I, Capellá G. Detection of genetic alterations in hereditary colorectal cancer screening. *Mutat Res* 2010; **693**: 19-31 [PMID: 19931546 DOI: 10.1016/j.mrfmmm.2009.11.002]

51 **Borràs E**, Pineda M, Blanco I, Jewett EM, Wang F, Teulé A, Caldés T, Urioste M, Martínez-Bouzas C, Brunet J, Balmaña J, Torres A, Ramón y Cajal T, Sanz J, Pérez-Cabornero L, Castellví-Bel S, Alonso A, Lanas A, González S, Moreno V, Gruber SB, Rosenberg NA, Mukherjee B, Lázaro C, Capellá G. MLH1 founder mutations with moderate penetrance in Spanish Lynch syndrome families. *Cancer Res* 2010; **70**: 7379-7391 [PMID: 20858721 DOI: 10.1158/0008-5472.CAN-10-0570]

52 **Mur P**, Pineda M, Romero A, Del Valle J, Borràs E, Canal A, Navarro M, Brunet J, Rueda D, Ramón Y Cajal T, Lázaro C, Caldés T, Blanco I, Soto JL, Capellá G. Identification of a founder EPCAM deletion in Spanish Lynch syndrome families. *Clin Genet* 2014; **85**: 260-266 [PMID: 23530899]

53 **Borelli I**, Barberis MA, Spina F, Casalis Cavalchini GC, Vivanet C, Balestrino L, Micheletti M, Allavena A, Sala P, Carcassi C, Pasini B. A unique MSH2 exon 8 deletion accounts for a major portion of all mismatch repair gene mutations in Lynch syndrome families of Sardinian origin. *Eur J Hum Genet* 2013; **21**: 154-161 [PMID: 22781090 DOI: 10.1038/ejhg.2012.150]

54 **Tomsic J**, Senter L, Liyanarachchi S, Clendenning M, Vaughn CP, Jenkins MA, Hopper JL, Young J, Samowitz W, de la Chapelle A. Recurrent and founder mutations in the PMS2 gene. *Clin Genet* 2013; **83**: 238-243 [PMID: 22577899 DOI: 10.1111/j.1399-0004.2012.01898.x]

55 **Scott RJ**, Lubinski J. Genetic epidemiology studies in hereditary non-polyposis colorectal cancer. *Methods Mol Biol* 2009; **472**: 89-102 [PMID: 19107430 DOI: 10.1007/978-1-60327-492-0_4]

56 **Bellido F**, Guinó E, Jagmohan-Changur S, Seguí N, Pineda M, Navarro M, Lázaro C, Blanco I, Vasen HF, Moreno V, Capellá G, Wijnen JT, Valle L. Genetic variant in the telomerase gene modifies cancer risk in Lynch syndrome. *Eur J Hum Genet* 2013; **21**: 511-516 [PMID: 22948024 DOI: 10.1038/ejhg.2012.204]

57 **Burn J**, Chapman P, Delhanty J, Wood C, Lalloo F, Cachon-Gonzalez MB, Tsioupra K, Church W, Rhodes M, Gunn A.

The UK Northern region genetic register for familial adenomatous polyposis coli: use of age of onset, congenital hypertrophy of the retinal pigment epithelium, and DNA markers in risk calculations. *J Med Genet* 1991; **28**: 289-296 [PMID: 1650842 DOI: 10.1136/jmg.28.5.289]

58 **Järvinen HJ**. Epidemiology of familial adenomatous polyposis in Finland: impact of family screening on the colorectal cancer rate and survival. *Gut* 1992; **33**: 357-360 [PMID: 1314763 DOI: 10.1136/gut.33.3.357]

59 **Bülow S**, Faurschou Nielsen T, Bülow C, Bisgaard ML, Karlsen L, Moesgaard F. The incidence rate of familial adenomatous polyposis. Results from the Danish Polyposis Register. *Int J Colorectal Dis* 1996; **11**: 88-91 [PMID: 8739833 DOI: 10.1007/BF00342466]

60 **de la Chapelle A**. Genetic predisposition to colorectal cancer. *Nat Rev Cancer* 2004; **4**: 769-780 [PMID: 15510158]

61 **Half E**, Bercovich D, Rozen P. Familial adenomatous polyposis. *Orphanet J Rare Dis* 2009; **4**: 22 [PMID: 19822006 DOI: 10.1186/1750-1172-4-22]

62 **Knudsen AL**, Bülow S, Tomlinson I, Möslein G, Heinimann K, Christensen IJ. Attenuated familial adenomatous polyposis: results from an international collaborative study. *Colorectal Dis* 2010; **12**: e243-e249 [PMID: 20105204 DOI: 10.1111/j.1463-1318.2010.02218.x]

63 **Fearon ER**, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990; **61**: 759-767 [PMID: 2188735 DOI: 10.1016/0092-8674(90)90186-I]

64 **Kinzler KW**, Vogelstein B. Lessons from hereditary colorectal cancer. *Cell* 1996; **87**: 159-170 [PMID: 8861899 DOI: 10.1016/S0092-8674(00)81333-1]

65 **Bisgaard ML**, Fenger K, Bülow S, Niebuhr E, Mohr J. Familial adenomatous polyposis (FAP): frequency, penetrance, and mutation rate. *Hum Mutat* 1994; **3**: 121-125 [PMID: 8199592 DOI: 10.1002/humu.1380030206]

66 **Hes FJ**, Nielsen M, Bik EC, Konvalinka D, Wijnen JT, Bakker E, Vasen HF, Breuning MH, Tops CM. Somatic APC mosaicism: an underestimated cause of polyposis coli. *Gut* 2008; **57**: 71-76 [PMID: 17604324 DOI: 10.1136/gut.2006.117796]

67 **Sieber OM**, Heinimann K, Gorman P, Lamlum H, Crabtree M, Simpson CA, Davies D, Neale K, Hodgson SV, Roylance RR, Phillips RK, Bodmer WF, Tomlinson IP. Analysis of chromosomal instability in human colorectal adenomas with two mutational hits at APC. *Proc Natl Acad Sci USA* 2002; **99**: 16910-16915 [PMID: 12486240 DOI: 10.1073/pnas.012679099]

68 **Aretz S**, Stienen D, Uhlhaas S, Pagenstecher C, Mangold E, Caspari R, Propping P, Friedl W. Large submicroscopic genomic APC deletions are a common cause of typical familial adenomatous polyposis. *J Med Genet* 2005; **42**: 185-192 [PMID: 15689459 DOI: 10.1136/jmg.2004.022822]

69 **Michils G**, Tejpar S, Thoelen R, van Cutsem E, Vermeesch JR, Fryns JP, Legius E, Matthijs G. Large deletions of the APC gene in 15% of mutation-negative patients with classical polyposis (FAP): a Belgian study. *Hum Mutat* 2005; **25**: 125-134 [PMID: 15643602 DOI: 10.1002/humu.20122]

70 **Lefevre JH**, Rodrigue CM, Mourra N, Bennis M, Flejou JF, Parc R, Tiret E, Gespach C, Parc YR. Implication of MYH in colorectal polyposis. *Ann Surg* 2006; **244**: 874-89; discussion 874-879 [PMID: 17122612 DOI: 10.1097/01.sla.0000246937.54435.50]

71 **Giardiello FM**, Brensinger JD, Petersen GM. AGA technical review on hereditary colorectal cancer and genetic testing. *Gastroenterology* 2001; **121**: 198-213 [PMID: 11438509 DOI: 10.1053/gast.2001.25581]

72 **Bunyan DJ**, Eccles DM, Sillibourne J, Wilkins E, Thomas NS, Shea-Simonds J, Duncan PJ, Curtis CE, Robinson DO, Harvey JF, Cross NC. Dosage analysis of cancer predisposition genes by multiplex ligation-dependent probe amplification. *Br J Cancer* 2004; **91**: 1155-1159 [PMID: 15475941 DOI: 10.1038/sj.bjc.6602121]

73 **Pilarski RT**, Brothman AR, Benn P, Shulman Rosengren S. Attenuated familial adenomatous polyposis in a man with an interstitial deletion of chromosome arm 5q. *Am J Med Genet* 1999; **86**: 321-324 [PMID: 10494086]

74 **Heald B**, Moran R, Milas M, Burke C, Eng C. Familial adenomatous polyposis in a patient with unexplained mental retardation. *Nat Clin Pract Neurol* 2007; **3**: 694-700 [PMID: 18046442 DOI: 10.1038/ncpneuro0658]

75 **Romero-Giménez J**, Dopeso H, Blanco I, Guerra-Moreno A, Gonzalez S, Vogt S, Aretz S, Schwartz S, Capella G, Arango D. Germline hypermethylation of the APC promoter is not a frequent cause of familial adenomatous polyposis in APC/MUTYH mutation negative families. *Int J Cancer* 2008; **122**: 1422-1425 [PMID: 18027849 DOI: 10.1002/ijc.23247]

76 **Castellsagué E**, González S, Guinó E, Stevens KN, Borràs E, Raymond VM, Lázaro C, Blanco I, Gruber SB, Capellá G. Allele-specific expression of APC in adenomatous polyposis families. *Gastroenterology* 2010; **139**: 439-447, 447.e1 [PMID: 20434453]

77 **Spier I**, Horpaopan S, Vogt S, Uhlhaas S, Morak M, Stienen D, Draaken M, Ludwig M, Holinski-Feder E, Nöthen MM, Hoffmann P, Aretz S. Deep intronic APC mutations explain a substantial proportion of patients with familial or early-onset adenomatous polyposis. *Hum Mutat* 2012; **33**: 1045-1050 [PMID: 22431159 DOI: 10.1002/humu.22082]

78 **Kadiyska TK**, Todorov TP, Bichev SN, Vazharova RV, Nossikoff AV, Savov AS, Mitev VI. APC promoter 1B deletion in familial polyposis--implications for mutation-negative families. *Clin Genet* 2014; **85**: 452-457 [PMID: 23725351 DOI: 10.1111/cge.12210]

79 **Nagase H**, Miyoshi Y, Horii A, Aoki T, Ogawa M, Utsunomiya J, Baba S, Sasazuki T, Nakamura Y. Correlation between the location of germ-line mutations in the APC gene and the number of colorectal polyps in familial adenomatous polyposis patients. *Cancer Res* 1992; **52**: 4055-4057 [PMID: 1319838]

80 **van der Luijt RB**, Vasen HF, Tops CM, Breukel C, Fodde R, Meera Khan P. APC mutation in the alternatively spliced region of exon 9 associated with late onset familial adenomatous polyposis. *Hum Genet* 1995; **96**: 705-710 [PMID: 8522331 DOI: 10.1007/BF00210303]

81 **Friedl W**, Meuschel S, Caspari R, Lamberti C, Krieger S, Sengteller M, Propping P. Attenuated familial adenomatous polyposis due to a mutation in the 3′ part of the APC gene. A clue for understanding the function of the APC protein. *Hum Genet* 1996; **97**: 579-584 [PMID: 8655134 DOI: 10.1007/BF02281864]

82 **Walon C**, Kartheuser A, Michils G, Smaers M, Lannoy N, Ngounou P, Mertens G, Verellen-Dumoulin C. Novel germline mutations in the APC gene and their phenotypic spectrum in familial adenomatous polyposis kindreds. *Hum Genet* 1997; **100**: 601-605 [PMID: 9341879 DOI: 10.1007/s004390050560]

83 **Soravia C**, Berk T, Madlensky L, Mitri A, Cheng H, Gallinger S, Cohen Z, Bapat B. Genotype-phenotype correlations in attenuated adenomatous polyposis coli. *Am J Hum Genet* 1998; **62**: 1290-1301 [PMID: 9585611 DOI: 10.1086/301883]

84 **Sieber OM**, Segditsas S, Knudsen AL, Zhang J, Luz J, Rowan AJ, Spain SL, Thirlwell C, Howarth KM, Jaeger EE, Robinson J, Volikos E, Silver A, Kelly G, Aretz S, Frayling I, Hutter P, Dunlop M, Guenther T, Neale K, Phillips R, Heinimann K, Tomlinson IP. Disease severity and genetic pathways in attenuated familial adenomatous polyposis vary greatly but depend on the site of the germline mutation. *Gut* 2006; **55**: 1440-1448 [PMID: 16461775 DOI: 10.1136/gut.2005.087106]

85 **Friedl W**, Aretz S. Familial adenomatous polyposis: experience from a study of 1164 unrelated german polyposis patients. *Hered Cancer Clin Pract* 2005; **3**: 95-114 [PMID: 20223039 DOI: 10.1186/1897-4287-3-3-95]

86 **Aretz S**, Stienen D, Friedrichs N, Stemmler S, Uhlhaas S, Rahner N, Propping P, Friedl W. Somatic APC mosaicism:

a frequent cause of familial adenomatous polyposis (FAP). *Hum Mutat* 2007; **28**: 985-992 [PMID: 17486639 DOI: 10.1002/humu.20549]

87 **Nielsen M**, Bik E, Hes FJ, Breuning MH, Vasen HF, Bakker E, Tops CM, Weiss MM. Genotype-phenotype correlations in 19 Dutch cases with APC gene deletions and a literature review. *Eur J Hum Genet* 2007; **15**: 1034-1042 [PMID: 17568392 DOI: 10.1038/sj.ejhg.5201871]

88 **Farrington SM**, Tenesa A, Barnetson R, Wiltshire A, Prendergast J, Porteous M, Campbell H, Dunlop MG. Germline susceptibility to colorectal cancer due to base-excision repair gene defects. *Am J Hum Genet* 2005; **77**: 112-119 [PMID: 15931596 DOI: 10.1086/431213]

89 **Cleary SP**, Cotterchio M, Jenkins MA, Kim H, Bristow R, Green R, Haile R, Hopper JL, LeMarchand L, Lindor N, Parfrey P, Potter J, Younghusband B, Gallinger S. Germline MutY human homologue mutations and colorectal cancer: a multisite case-control study. *Gastroenterology* 2009; **136**: 1251-1260 [PMID: 19245865 DOI: 10.1053/j.gastro.2008.12.050]

90 **Nielsen M**, Joerink-van de Beld MC, Jones N, Vogt S, Tops CM, Vasen HF, Sampson JR, Aretz S, Hes FJ. Analysis of MUTYH genotypes and colorectal phenotypes in patients With MUTYH-associated polyposis. *Gastroenterology* 2009; **136**: 471-476 [PMID: 19032956 DOI: 10.1053/j.gastro.2008.10.056]

91 **Morak M**, Laner A, Bacher U, Keiling C, Holinski-Feder E. MUTYH-associated polyposis - variability of the clinical phenotype in patients with biallelic and monoallelic MUTYH mutations and report on novel mutations. *Clin Genet* 2010; **78**: 353-363 [PMID: 20618354 DOI: 10.1111/j.1399-0004.2010.01478.x]

92 **Out AA**, Tops CM, Nielsen M, Weiss MM, van Minderhout IJ, Fokkema IF, Buisine MP, Claes K, Colas C, Fodde R, Fostira F, Franken PF, Gaustadnes M, Heinimann K, Hodgson SV, Hogervorst FB, Holinski-Feder E, Lagerstedt-Robinson K, Olschwang S, van den Ouweland AM, Redeker EJ, Scott RJ, Vankeirsbilck B, Grønlund RV, Wijnen JT, Wikman FP, Aretz S, Sampson JR, Devilee P, den Dunnen JT, Hes FJ. Leiden Open Variation Database of the MUTYH gene. *Hum Mutat* 2010; **31**: 1205-1215 [PMID: 20725929 DOI: 10.1002/humu.21343]

93 **Sieber OM**, Lipton L, Crabtree M, Heinimann K, Fidalgo P, Phillips RK, Bisgaard ML, Orntoft TF, Aaltonen LA, Hodgson SV, Thomas HJ, Tomlinson IP. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. *N Engl J Med* 2003; **348**: 791-799 [PMID: 12606733 DOI: 10.1056/NEJMoa025283]

94 **Ponti G**, Ponz de Leon M, Maffei S, Pedroni M, Losi L, Di Gregorio C, Gismondi V, Scarselli A, Benatti P, Roncari B, Seidenari S, Pellacani G, Varotti C, Prete E, Varesco L, Roncucci L. Attenuated familial adenomatous polyposis and Muir-Torre syndrome linked to compound biallelic constitutional MYH gene mutations. *Clin Genet* 2005; **68**: 442-447 [PMID: 16207212 DOI: 10.1111/j.1399-0004.2005.00519.x]

95 **Aretz S**, Uhlhaas S, Goergens H, Siberg K, Vogel M, Pagenstecher C, Mangold E, Caspari R, Propping P, Friedl W. MUTYH-associated polyposis: 70 of 71 patients with biallelic mutations present with an attenuated or atypical phenotype. *Int J Cancer* 2006; **119**: 807-814 [PMID: 16557584 DOI: 10.1002/ijc.21905]

96 **Nielsen M**, Poley JW, Verhoef S, van Puijenbroek M, Weiss MM, Burger GT, Dommering CJ, Vasen HF, Kuipers EJ, Wagner A, Morreau H, Hes FJ. Duodenal carcinoma in MUTYH-associated polyposis. *J Clin Pathol* 2006; **59**: 1212-1215 [PMID: 16943222 DOI: 10.1136/jcp.2005.031757]

97 **Vogt S**, Jones N, Christian D, Engel C, Nielsen M, Kaufmann A, Steinke V, Vasen HF, Propping P, Sampson JR, Hes FJ, Aretz S. Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. *Gastroenterology* 2009; **137**: 1976-85. e1-10 [PMID: 19732775]

98 **Nielsen M**, Morreau H, Vasen HF, Hes FJ. MUTYH-associated polyposis (MAP). *Crit Rev Oncol Hematol* 2011; **79**: 1-16 [PMID: 20663686 DOI: 10.1016/j.critrevonc.2010.05.011]

99 **Grover S**, Kastrinos F, Steyerberg EW, Cook EF, Dewanwala A, Burbidge LA, Wenstrup RJ, Syngal S. Prevalence and phenotypes of APC and MUTYH mutations in patients with multiple colorectal adenomas. *JAMA* 2012; **308**: 485-492 [PMID: 22851115 DOI: 10.1001/jama.2012.8780]

100 **Shibutani S**, Takeshita M, Grollman AP. Insertion of specific bases during DNA synthesis past the oxidation-damaged base 8-oxodG. *Nature* 1991; **349**: 431-434 [PMID: 1992344 DOI: 10.1038/349431a0]

101 **Lipton L**, Halford SE, Johnson V, Novelli MR, Jones A, Cummings C, Barclay E, Sieber O, Sadat A, Bisgaard ML, Hodgson SV, Aaltonen LA, Thomas HJ, Tomlinson IP. Carcinogenesis in MYH-associated polyposis follows a distinct genetic pathway. *Cancer Res* 2003; **63**: 7595-7599 [PMID: 14633673]

102 **Nielsen M**, de Miranda NF, van Puijenbroek M, Jordanova ES, Middeldorp A, van Wezel T, van Eijk R, Tops CM, Vasen HF, Hes FJ, Morreau H. Colorectal carcinomas in MUTYH-associated polyposis display histopathological similarities to microsatellite unstable carcinomas. *BMC Cancer* 2009; **9**: 184 [PMID: 19527492 DOI: 10.1186/1471-2407-9-184]

103 **van Puijenbroek M**, Nielsen M, Tops CM, Halfwerk H, Vasen HF, Weiss MM, van Wezel T, Hes FJ, Morreau H. Identification of patients with (atypical) MUTYH-associated polyposis by KRAS2 c.34G > T prescreening followed by MUTYH hotspot analysis in formalin-fixed paraffin-embedded tissue. *Clin Cancer Res* 2008; **14**: 139-142 [PMID: 18172263 DOI: 10.1158/1078-0432.CCR-07-1705]

104 **Gismondi V**, Meta M, Bonelli L, Radice P, Sala P, Bertario L, Viel A, Fornasarig M, Arrigoni A, Gentile M, Ponz de Leon M, Anselmi L, Mareni C, Bruzzi P, Varesco L. Prevalence of the Y165C, G382D and 1395delGGA germline mutations of the MYH gene in Italian patients with adenomatous polyposis coli and colorectal adenomas. *Int J Cancer* 2004; **109**: 680-684 [PMID: 14999774 DOI: 10.1002/ijc.20054]

105 **Nielsen M**, Franken PF, Reinards TH, Weiss MM, Wagner A, van der Klift H, Kloosterman S, Houwing-Duistermaat JJ, Aalfs CM, Ausems MG, Bröcker-Vriends AH, Gomez Garcia EB, Hoogerbrugge N, Menko FH, Sijmons RH, Verhoef S, Kuipers EJ, Morreau H, Breuning MH, Tops CM, Wijnen JT, Vasen HF, Fodde R, Hes FJ. Multiplicity in polyp count and extracolonic manifestations in 40 Dutch patients with MYH associated polyposis coli (MAP). *J Med Genet* 2005; **42**: e54 [PMID: 16140997 DOI: 10.1136/jmg.2005.033217]

106 **Dolwani S**, Williams GT, West KP, Newman J, Stock D, Griffiths AP, Best J, Cheadle JP, Sampson JR. Analysis of inherited MYH/(MutYH) mutations in British Asian patients with colorectal cancer. *Gut* 2007; **56**: 593 [PMID: 17369389 DOI: 10.1136/gut.2006.094532]

107 **Kim JC**, Ka IH, Lee YM, Koo KH, Kim HC, Yu CS, Jang SJ, Kim YS, Lee HI, Lee KH. MYH, OGG1, MTH1, and APC alterations involved in the colorectal tumorigenesis of Korean patients with multiple adenomas. *Virchows Arch* 2007; **450**: 311-319 [PMID: 17252231 DOI: 10.1007/s00428-006-0363-6]

108 **Yanaru-Fujisawa R**, Matsumoto T, Ushijima Y, Esaki M, Hirahashi M, Gushima M, Yao T, Nakabeppu Y, Iida M. Genomic and functional analyses of MUTYH in Japanese patients with adenomatous polyposis. *Clin Genet* 2008; **73**: 545-553 [PMID: 18422726 DOI: 10.1111/j.1399-0004.2008.00998.x]

109 **Gómez-Fernández N**, Castellví-Bel S, Fernández-Rozadilla C, Balaguer F, Muñoz J, Madrigal I, Milà M, Graña B, Vega A, Castells A, Carracedo A, Ruiz-Ponte C. Molecular analysis of the APC and MUTYH genes in Galician and Catalonian FAP families: a different spectrum of mutations? *BMC Med Genet* 2009; **10**: 57 [PMID: 19531215 DOI: 10.1186/1471-2350-10-57]

110 **Prior TW**, Bridgeman SJ. Identifying mutations for MYH-associated polyposis. *Curr Protoc Hum Genet* 2010; **Chapter 10**: Unit 10.13 [PMID: 20063264]

111 **Abdelmaksoud-Dammak R**, Miladi-Abdennadher I, Amouri A, Tahri N, Ayadi L, Khabir A, Frikha F, Gargouri A, Mokdad-Gargouri R. High prevalence of the c.1227_1228dup (p.Glu410GlyfsX43) mutation in Tunisian families affected with MUTYH-associated-polyposis. *Fam Cancer* 2012; **11**: 503-508 [PMID: 22744763 DOI: 10.1007/s10689-012-9543-5]

112 **Palles C**, Cazier JB, Howarth KM, Domingo E, Jones AM, Broderick P, Kemp Z, Spain SL, Guarino E, Salguero I, Sherborne A, Chubb D, Carvajal-Carmona LG, Ma Y, Kaur K, Dobbins S, Barclay E, Gorman M, Martin L, Kovac MB, Humphray S, Lucassen A, Holmes CC, Bentley D, Donnelly P, Taylor J, Petridis C, Roylance R, Sawyer EJ, Kerr DJ, Clark S, Grimes J, Kearsey SE, Thomas HJ, McVean G, Houlston RS, Tomlinson I. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. *Nat Genet* 2013; **45**: 136-144 [PMID: 23263490]

113 **Valle L**, Hernández-Illán E, Bellido F, Aiza G, Castillejo A, Castillejo MI, Navarro M, Seguí N, Vargas G, Guarinos C, Juarez M, Sanjuán X, Iglesias S, Alenda C, Egoavil C, Segura A, Juan MJ, Rodriguez-Soler M, Brunet J, González S, Jover R, Lázaro C, Capellá G, Pineda M, Soto JL, Blanco I. New insights into POLE and POLD1 germline mutations in familial colorectal cancer and polyposis. *Hum Mol Genet* 2014; **23**: 3506-3512 [PMID: 24501277 DOI: 10.1093/hmg/ddu058]

114 **Donehower LA**, Creighton CJ, Schultz N, Shinbrot E, Chang K, Gunaratne PH, Muzny D, Sander C, Hamilton SR, Gibbs RA, Wheeler D. MLH1-silenced and non-silenced subgroups of hypermutated colorectal carcinomas have distinct mutational landscapes. *J Pathol* 2013; **229**: 99-110 [PMID: 22899370 DOI: 10.1002/path.4087]

115 **Church DN**, Briggs SE, Palles C, Domingo E, Kearsey SJ, Grimes JM, Gorman M, Martin L, Howarth KM, Hodgson SV, Kaur K, Taylor J, Tomlinson IP. DNA polymerase ε and δ exonuclease domain mutations in endometrial cancer. *Hum Mol Genet* 2013; **22**: 2820-2828 [PMID: 23528559 DOI: 10.1093/hmg/ddt131]

116 **Briggs S**, Tomlinson I. Germline and somatic polymerase epsilon and delta mutations define a new class of hypermutated colorectal and endometrial cancers. *J Pathol* 2013; **230**: 148-153 [PMID: 23447401 DOI: 10.1002/path.4185]

117 **Whitelaw SC**, Murday VA, Tomlinson IP, Thomas HJ, Cottrell S, Ginsberg A, Bukofzer S, Hodgson SV, Skudowitz RB, Jass JR, Talbot IC, Northover JM, Bodmer WF, Solomon E. Clinical and molecular features of the hereditary mixed polyposis syndrome. *Gastroenterology* 1997; **112**: 327-334 [PMID: 9024286 DOI: 10.1053/gast.1997.v112.pm9024286]

118 **Tomlinson I**, Rahman N, Frayling I, Mangion J, Barfoot R, Hamoudi R, Seal S, Northover J, Thomas HJ, Neale K, Hodgson S, Talbot I, Houlston R, Stratton MR. Inherited susceptibility to colorectal adenomas and carcinomas: evidence for a new predisposition gene on 15q14-q22. *Gastroenterology* 1999; **116**: 789-795 [PMID: 10092300 DOI: 10.1016/S0016-5085(99)70061-2]

119 **Jaeger EE**, Woodford-Richens KL, Lockett M, Rowan AJ, Sawyer EJ, Heinimann K, Rozen P, Murday VA, Whitelaw SC, Ginsberg A, Atkin WS, Lynch HT, Southey MC, Debinski H, Eng C, Bodmer WF, Talbot IC, Hodgson SV, Thomas HJ, Tomlinson IP. An ancestral Ashkenazi haplotype at the HMPS/CRAC1 locus on 15q13-q14 is associated with hereditary mixed polyposis syndrome. *Am J Hum Genet* 2003; **72**: 1261-1267 [PMID: 12696020 DOI: 10.1086/375144]

120 **Jaeger E**, Webb E, Howarth K, Carvajal-Carmona L, Rowan A, Broderick P, Walther A, Spain S, Pittman A, Kemp Z, Sullivan K, Heinimann K, Lubbe S, Domingo E, Barclay E, Martin L, Gorman M, Chandler I, Vijayakrishnan J, Wood W, Papaemmanuil E, Penegar S, Qureshi M, Farrington S, Tenesa A, Cazier JB, Kerr D, Gray R, Peto J, Dunlop M, Campbell H, Thomas H, Houlston R, Tomlinson I. Common genetic variants at the CRAC1 (HMPS) locus on chromosome 15q13.3 influence colorectal cancer risk. *Nat Genet* 2008; **40**: 26-28 [PMID: 18084292 DOI: 10.1038/ng.2007.41]

121 **Jaeger E**, Leedham S, Lewis A, Segditsas S, Becker M, Cuadrado PR, Davis H, Kaur K, Heinimann K, Howarth K, East J, Taylor J, Thomas H, Tomlinson I. 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* 2012; **44**: 699-703 [PMID: 22561515 DOI: 10.1038/ng.2263]

122 **Gatalica Z**, Torlakovic E. Pathology of the hereditary colorectal carcinoma. *Fam Cancer* 2008; **7**: 15-26 [PMID: 17564815 DOI: 10.1007/s10689-007-9146-8]

123 **Sachatello CR**, Hahn IS, Carrington CB. Juvenile gastrointestinal polyposis in a female infant: report of a case and review of the literature of a recently recognized syndrome. *Surgery* 1974; **75**: 107-114 [PMID: 4543470]

124 **Jass JR**, Williams CB, Bussey HJ, Morson BC. Juvenile polyposis--a precancerous condition. *Histopathology* 1988; **13**: 619-630 [PMID: 2853131 DOI: 10.1111/j.1365-2559.1988.tb02093.x]

125 **Giardiello FM**, Hamilton SR, Kern SE, Offerhaus GJ, Green PA, Celano P, Krush AJ, Booker SV. Colorectal neoplasia in juvenile polyposis or juvenile polyps. *Arch Dis Child* 1991; **66**: 971-975 [PMID: 1656892 DOI: 10.1136/adc.66.8.971]

126 **Howe JR**, Mitros FA, Summers RW. The risk of gastrointestinal carcinoma in familial juvenile polyposis. *Ann Surg Oncol* 1998; **5**: 751-756 [PMID: 9869523 DOI: 10.1007/BF02303487]

127 **Sayed MG**, Ahmed AF, Ringold JR, Anderson ME, Bair JL, Mitros FA, Lynch HT, Tinley ST, Petersen GM, Giardiello FM, Vogelstein B, Howe JR. Germline SMAD4 or BMPR1A mutations and phenotype of juvenile polyposis. *Ann Surg Oncol* 2002; **9**: 901-906 [PMID: 12417513 DOI: 10.1007/BF02557528]

128 **Howe JR**, Sayed MG, Ahmed AF, Ringold J, Larsen-Haidle J, Merg A, Mitros FA, Vaccaro CA, Petersen GM, Giardiello FM, Tinley ST, Aaltonen LA, Lynch HT. The prevalence of MADH4 and BMPR1A mutations in juvenile polyposis and absence of BMPR2, BMPR1B, and ACVR1 mutations. *J Med Genet* 2004; **41**: 484-491 [PMID: 15235019 DOI: 10.1136/jmg.2004.018598]

129 **Friedl W**, Uhlhaas S, Schulmann K, Stolte M, Loff S, Back W, Mangold E, Stern M, Knaebel HP, Sutter C, Weber RG, Pistorius S, Burger B, Propping P. Juvenile polyposis: massive gastric polyposis is more common in MADH4 mutation carriers than in BMPR1A mutation carriers. *Hum Genet* 2002; **111**: 108-111 [PMID: 12136244 DOI: 10.1007/s00439-002-0748-9]

130 **O'Malley M**, LaGuardia L, Kalady MF, Parambil J, Heald B, Eng C, Church J, Burke CA. The prevalence of hereditary hemorrhagic telangiectasia in juvenile polyposis syndrome. *Dis Colon Rectum* 2012; **55**: 886-892 [PMID: 22810475 DOI: 10.1097/DCR.0b013e31825aad32]

131 **Sweet K**, Willis J, Zhou XP, Gallione C, Sawada T, Alhopuro P, Khoo SK, Patocs A, Martin C, Bridgeman S, Heinz J, Pilarski R, Lehtonen R, Prior TW, Frebourg T, Teh BT, Marchuk DA, Aaltonen LA, Eng C. Molecular classification of patients with unexplained hamartomatous and hyperplastic polyposis. *JAMA* 2005; **294**: 2465-2473 [PMID: 16287957 DOI: 10.1001/jama.294.19.2465]

132 **Gallione CJ**, Repetto GM, Legius E, Rustgi AK, Schelley SL, Tejpar S, Mitchell G, Drouin E, Westermann CJ, Marchuk DA. A combined syndrome of juvenile polyposis and hereditary haemorrhagic telangiectasia associated with mutations in MADH4 (SMAD4). *Lancet* 2004; **363**: 852-859 [PMID: 15031030 DOI: 10.1016/S0140-6736(04)15732-2]

133 **Howe JR**, Haidle JL, Lal G, Bair J, Song C, Pechman B, Chinnathambi S, Lynch HT. ENG mutations in MADH4/BMPR1A mutation negative patients with juvenile polyposis.

Clin Genet 2007; **71**: 91-92 [PMID: 17204053 DOI: 10.1111/j.1399-0004.2007.00734.x]
134 **van Hattem WA**, Brosens LA, de Leng WW, Morsink FH, Lens S, Carvalho R, Giardiello FM, Offerhaus GJ. Large genomic deletions of SMAD4, BMPR1A and PTEN in juvenile polyposis. *Gut* 2008; **57**: 623-627 [PMID: 18178612 DOI: 10.1136/gut.2007.142927]
135 **Eng C**, Ji H. Molecular classification of the inherited hamartoma polyposis syndromes: clearing the muddied waters. *Am J Hum Genet* 1998; **62**: 1020-1022 [PMID: 9545417 DOI: 10.1086/301847]
136 **Dahdaleh FS**, Carr JC, Calva D, Howe JR. Juvenile polyposis and other intestinal polyposis syndromes with microdeletions of chromosome 10q22-23. *Clin Genet* 2012; **81**: 110-116 [PMID: 21834858 DOI: 10.1111/j.1399-0004.2011.01763.x]
137 **Beggs AD**, Latchford AR, Vasen HF, Moslein G, Alonso A, Aretz S, Bertario L, Blanco I, Bülow S, Burn J, Capella G, Colas C, Friedl W, Møller P, Hes FJ, Järvinen H, Mecklin JP, Nagengast FM, Parc Y, Phillips RK, Hyer W, Ponz de Leon M, Renkonen-Sinisalo L, Sampson JR, Stormorken A, Tejpar S, Thomas HJ, Wijnen JT, Clark SK, Hodgson SV. Peutz-Jeghers syndrome: a systematic review and recommendations for management. *Gut* 2010; **59**: 975-986 [PMID: 20581245 DOI: 10.1136/gut.2009.198499]
138 **Erbe RW**. Inherited gastrointestinal-polyposis syndromes. *N Engl J Med* 1976; **294**: 1101-1104 [PMID: 768769 DOI: 10.1056/NEJM197605132942007]
139 **Higham P**, Alawi F, Stoopler ET. Medical management update: Peutz Jeghers syndrome. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2010; **109**: 5-11 [PMID: 20123375 DOI: 10.1016/j.tripleo.2009.08.022]
140 **Boardman LA**, Thibodeau SN, Schaid DJ, Lindor NM, McDonnell SK, Burgart LJ, Ahlquist DA, Podratz KC, Pittelkow M, Hartmann LC. Increased risk for cancer in patients with the Peutz-Jeghers syndrome. *Ann Intern Med* 1998; **128**: 896-899 [PMID: 9634427 DOI: 10.7326/0003-4819-128-11-199806010-00004]
141 **Choi HS**, Park YJ, Youk EG, Yoon KA, Ku JL, Kim NK, Kim SM, Kim YJ, Moon DJ, Min JS, Park CJ, Bae OS, Yang DH, Jun SH, Chung ES, Jung PM, Whang Y, Park JG. Clinical characteristics of Peutz-Jeghers syndrome in Korean polyposis patients. *Int J Colorectal Dis* 2000; **15**: 35-38 [PMID: 10766089 DOI: 10.1007/s003840050005]
142 **Lim W**, Olschwang S, Keller JJ, Westerman AM, Menko FH, Boardman LA, Scott RJ, Trimbath J, Giardiello FM, Gruber SB, Gille JJ, Offerhaus GJ, de Rooij FW, Wilson JH, Spigelman AD, Phillips RK, Houlston RS. Relative frequency and morphology of cancers in STK11 mutation carriers. *Gastroenterology* 2004; **126**: 1788-1794 [PMID: 15188174 DOI: 10.1053/j.gastro.2004.03.014]
143 **Hearle N**, Schumacher V, Menko FH, Olschwang S, Boardman LA, Gille JJ, Keller JJ, Westerman AM, Scott RJ, Lim W, Trimbath JD, Giardiello FM, Gruber SB, Offerhaus GJ, de Rooij FW, Wilson JH, Hansmann A, Möslein G, Royer-Pokora B, Vogel T, Phillips RK, Spigelman AD, Houlston RS. Frequency and spectrum of cancers in the Peutz-Jeghers syndrome. *Clin Cancer Res* 2006; **12**: 3209-3215 [PMID: 16707622 DOI: 10.1158/1078-0432.CCR-06-0083]
144 **Young RH**. Sex cord-stromal tumors of the ovary and testis: their similarities and differences with consideration of selected problems. *Mod Pathol* 2005; **18** Suppl 2: S81-S98 [PMID: 15502809 DOI: 10.1038/modpathol.3800311]
145 **Aretz S**, Stienen D, Uhlhaas S, Loff S, Back W, Pagenstecher C, McLeod DR, Graham GE, Mangold E, Santer R, Propping P, Friedl W. High proportion of large genomic STK11 deletions in Peutz-Jeghers syndrome. *Hum Mutat* 2005; **26**: 513-519 [PMID: 16287113 DOI: 10.1002/humu.20253]
146 **Mester J**, Eng C. When overgrowth bumps into cancer: the PTEN-opathies. *Am J Med Genet C Semin Med Genet* 2013; **163C**: 114-121 [PMID: 23613428 DOI: 10.1002/ajmg.c.31364]
147 **Orloff MS**, Eng C. Genetic and phenotypic heterogeneity in the PTEN hamartoma tumour syndrome. *Oncogene* 2008; **27**: 5387-5397 [PMID: 18794875 DOI: 10.1038/onc.2008.237]
148 **Tan MH**, Mester J, Peterson C, Yang Y, Chen JL, Rybicki LA, Milas K, Pederson H, Remzi B, Orloff MS, Eng C. 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* 2011; **88**: 42-56 [PMID: 21194675 DOI: 10.1016/j.ajhg.2010.11.013]
149 **Lachlan KL**, Lucassen AM, Bunyan D, Temple IK. Cowden syndrome and Bannayan Riley Ruvalcaba syndrome represent one condition with variable expression and age-related penetrance: results of a clinical study of PTEN mutation carriers. *J Med Genet* 2007; **44**: 579-585 [PMID: 17526800 DOI: 10.1136/jmg.2007.049981]
150 **Tan MH**, Mester JL, Ngeow J, Rybicki LA, Orloff MS, Eng C. Lifetime cancer risks in individuals with germline PTEN mutations. *Clin Cancer Res* 2012; **18**: 400-407 [PMID: 22252256 DOI: 10.1158/1078-0432.CCR-11-2283]
151 **Nieuwenhuis MH**, Kets CM, Murphy-Ryan M, Yntema HG, Evans DG, Colas C, Møller P, Hes FJ, Hodgson SV, Olderode-Berends MJ, Aretz S, Heinimann K, Gómez García EB, Douglas F, Spigelman A, Timshel S, Lindor NM, Vasen HF. Cancer risk and genotype-phenotype correlations in PTEN hamartoma tumor syndrome. *Fam Cancer* 2014; **13**: 57-63 [PMID: 23934601 DOI: 10.1007/s10689-013-9674-3]
152 **Goffin A**, Hoefsloot LH, Bosgoed E, Swillen A, Fryns JP. PTEN mutation in a family with Cowden syndrome and autism. *Am J Med Genet* 2001; **105**: 521-524 [PMID: 11496368 DOI: 10.1002/ajmg.1477]
153 **Herman GE**, Butter E, Enrile B, Pastore M, Prior TW, Sommer A. Increasing knowledge of PTEN germline mutations: Two additional patients with autism and macrocephaly. *Am J Med Genet A* 2007; **143**: 589-593 [PMID: 17286265 DOI: 10.1002/ajmg.a.31619]
154 **Herman GE**, Henninger N, Ratliff-Schaub K, Pastore M, Fitzgerald S, McBride KL. Genetic testing in autism: how much is enough? *Genet Med* 2007; **9**: 268-274 [PMID: 17505203 DOI: 10.1097/GIM.0b013e31804d683b]
155 **Orrico A**, Galli L, Buoni S, Orsi A, Vonella G, Sorrentino V. Novel PTEN mutations in neurodevelopmental disorders and macrocephaly. *Clin Genet* 2009; **75**: 195-198 [PMID: 18759867 DOI: 10.1111/j.1399-0004.2008.01074.x]
156 **Varga EA**, Pastore M, Prior T, Herman GE, McBride KL. The prevalence of PTEN mutations in a clinical pediatric cohort with autism spectrum disorders, developmental delay, and macrocephaly. *Genet Med* 2009; **11**: 111-117 [PMID: 19265751 DOI: 10.1097/GIM.0b013e31818fd762]
157 **Bennett KL**, Mester J, Eng C. Germline epigenetic regulation of KILLIN in Cowden and Cowden-like syndrome. *JAMA* 2010; **304**: 2724-2731 [PMID: 21177507 DOI: 10.1001/jama.2010.1877]
158 **Thompson BA**, Spurdle AB, Plazzer JP, Greenblatt MS, Akagi K, Al-Mulla F, Bapat B, Bernstein I, Capellá G, den Dunnen JT, du Sart D, Fabre A, Farrell MP, Farrington SM, Frayling IM, Frebourg T, Goldgar DE, Heinen CD, Holinski-Feder E, Kohonen-Corish M, Robinson KL, Leung SY, Martins A, Moller P, Morak M, Nystrom M, Peltomaki P, Pineda M, Qi M, Ramesar R, Rasmussen LJ, Royer-Pokora B, Scott RJ, Sijmons R, Tavtigian SV, Tops CM, Weber T, Wijnen J, Woods MO, Macrae F, Genuardi M. Application of a 5-tiered scheme for standardized classification of 2,360 unique mismatch repair gene variants in the InSiGHT locus-specific database. *Nat Genet* 2014; **46**: 107-115 [PMID: 24362816]
159 **Hofstra RM**, Spurdle AB, Eccles D, Foulkes WD, de Wind N, Hoogerbrugge N, Hogervorst FB. Tumor characteristics as an analytic tool for classifying genetic variants of uncertain clinical significance. *Hum Mutat* 2008; **29**: 1292-1303 [PMID: 18951447 DOI: 10.1002/humu.20894]
160 **Menéndez M**, González S, Obrador-Hevia A, Domínguez

A, Pujol MJ, Valls J, Canela N, Blanco I, Torres A, Pineda-Lucena A, Moreno V, Bachs O, Capellá G. Functional characterization of the novel APC N1026S variant associated with attenuated familial adenomatous polyposis. *Gastroenterology* 2008; **134**: 56-64 [PMID: 18166348 DOI: 10.1053/j.gastro.2007.10.009]

161 **Perera S**, Li B, Tsitsikotas S, Ramyar L, Pollett A, Semotiuk K, Bapat B. A novel and rapid method of determining the effect of unclassified MLH1 genetic variants on differential allelic expression. *J Mol Diagn* 2010; **12**: 757-764 [PMID: 20864636 DOI: 10.2353/jmoldx.2010.090240]

162 **Borràs E**, Pineda M, Brieger A, Hinrichsen I, Gómez C, Navarro M, Balmaña J, Ramón y Cajal T, Torres A, Brunet J, Blanco I, Plotz G, Lázaro C, Capellá G. Comprehensive functional assessment of MLH1 variants of unknown significance. *Hum Mutat* 2012; **33**: 1576-1588 [PMID: 22736432 DOI: 10.1002/humu.22142]

163 **Borràs E**, Pineda M, Cadiñanos J, Del Valle J, Brieger A, Hinrichsen I, Cabanillas R, Navarro M, Brunet J, Sanjuan X, Musulen E, van der Klift H, Lázaro C, Plotz G, Blanco I, Capellá G. Refining the role of PMS2 in Lynch syndrome: germline mutational analysis improved by comprehensive assessment of variants. *J Med Genet* 2013; **50**: 552-563 [PMID: 23709753 DOI: 10.1136/jmedgenet-2012-101511]

164 **Heinen CD**, Juel Rasmussen L. Determining the functional significance of mismatch repair gene missense variants using biochemical and cellular assays. *Hered Cancer Clin Pract* 2012; **10**: 9 [PMID: 22824075 DOI: 10.1186/1897-4287-10-9]

165 **Dowty JG**, Win AK, Buchanan DD, Lindor NM, Macrae FA, Clendenning M, Antill YC, Thibodeau SN, Casey G, Gallinger S, Marchand LL, Newcomb PA, Haile RW, Young GP, James PA, Giles GG, Gunawardena SR, Leggett BA, Gattas M, Boussioutas A, Ahnen DJ, Baron JA, Parry S, Goldblatt J, Young JP, Hopper JL, Jenkins MA. Cancer risks for MLH1 and MSH2 mutation carriers. *Hum Mutat* 2013; **34**: 490-497 [PMID: 23255516 DOI: 10.1002/humu.22262]

166 **Nilbert M**, Timshel S, Bernstein I, Larsen K. Role for genetic anticipation in Lynch syndrome. *J Clin Oncol* 2009; **27**: 360-364 [PMID: 19075283 DOI: 10.1200/JCO.2008.16.1281]

167 **Boonstra PS**, Gruber SB, Raymond VM, Huang SC, Timshel S, Nilbert M, Mukherjee B. A review of statistical methods for testing genetic anticipation: looking for an answer in Lynch syndrome. *Genet Epidemiol* 2010; **34**: 756-768 [PMID: 20878717 DOI: 10.1002/gepi.20534]

168 **Boonstra PS**, Mukherjee B, Taylor JM, Nilbert M, Moreno V, Gruber SB. Bayesian modeling for genetic anticipation in presence of mutational heterogeneity: a case study in Lynch syndrome. *Biometrics* 2011; **67**: 1627-1637 [PMID: 21627626 DOI: 10.1111/j.1541-0420.2011.01607.x]

169 **Gruber SB**, Mukherjee B. Anticipation in lynch syndrome: still waiting for the answer. *J Clin Oncol* 2009; **27**: 326-327 [PMID: 19075261 DOI: 10.1200/JCO.2008.19.1445]

170 **Coolbaugh-Murphy MI**, Xu JP, Ramagli LS, Ramagli BC, Brown BW, Lynch PM, Hamilton SR, Frazier ML, Siciliano MJ. Microsatellite instability in the peripheral blood leukocytes of HNPCC patients. *Hum Mutat* 2010; **31**: 317-324 [PMID: 20052760 DOI: 10.1002/humu.21190]

171 **Seguí N**, Pineda M, Guinó E, Borràs E, Navarro M, Bellido F, Moreno V, Lázaro C, Blanco I, Capellá G, Valle L. Telomere length and genetic anticipation in Lynch syndrome. *PLoS One* 2013; **8**: e61286 [PMID: 23637804]

172 **Timshel S**, Therkildsen C, Bendahl PO, Bernstein I, Nilbert M. An effect from anticipation also in hereditary nonpolyposis colorectal cancer families without identified mutations. *Cancer Epidemiol* 2009; **33**: 231-234 [PMID: 19748845 DOI: 10.1016/j.canep.2009.06.007]

173 **Peters U**, Jiao S, Schumacher FR, Hutter CM, Aragaki AK, Baron JA, Berndt SI, Bézieau S, Brenner H, Butterbach K, Caan BJ, Campbell PT, Carlson CS, Casey G, Chan AT, Chang-Claude J, Chanock SJ, Chen LS, Coetzee GA, Coetzee SG, Conti DV, Curtis KR, Duggan D, Edwards T, Fuchs CS, Gallinger S, Giovannucci EL, Gogarten SM, Gruber SB, Haile RW, Harrison TA, Hayes RB, Henderson BE, Hoffmeister M, Hopper JL, Hudson TJ, Hunter DJ, Jackson RD, Jee SH, Jenkins MA, Jia WH, Kolonel LN, Kooperberg C, Küry S, Lacroix AZ, Laurie CC, Laurie CA, Le Marchand L, Lemire M, Levine D, Lindor NM, Liu Y, Ma J, Makar KW, Matsuo K, Newcomb PA, Potter JD, Prentice RL, Qu C, Rohan T, Rosse SA, Schoen RE, Seminara D, Shrubsole M, Shu XO, Slattery ML, Taverna D, Thibodeau SN, Ulrich CM, White E, Xiang Y, Zanke BW, Zeng YX, Zhang B, Zheng W, Hsu L. Identification of Genetic Susceptibility Loci for Colorectal Tumors in a Genome-Wide Meta-analysis. *Gastroenterology* 2013; **144**: 799-807.e24 [PMID: 23266556]

174 **Houlston RS**, Cheadle J, Dobbins SE, Tenesa A, Jones AM, Howarth K, Spain SL, Broderick P, Domingo E, Farrington S, Prendergast JG, Pittman AM, Theodoratou E, Smith CG, Olver B, Walther A, Barnetson RA, Churchman M, Jaeger EE, Penegar S, Barclay E, Martin L, Gorman M, Mager R, Johnstone E, Midgley R, Niittymäki I, Tuupanen S, Colley J, Idziaszczyk S, Thomas HJ, Lucassen AM, Evans DG, Maher ER, Maughan T, Dimas A, Dermitzakis E, Cazier JB, Aaltonen LA, Pharoah P, Kerr DJ, Carvajal-Carmona LG, Campbell H, Dunlop MG, Tomlinson IP. Meta-analysis of three genome-wide association studies identifies susceptibility loci for colorectal cancer at 1q41, 3q26.2, 12q13.13 and 20q13.33. *Nat Genet* 2010; **42**: 973-977 [PMID: 20972440 DOI: 10.1038/ng.670]

175 **Jiao S**, Hsu L, Berndt S, Bézieau S, Brenner H, Buchanan D, Caan BJ, Campbell PT, Carlson CS, Casey G, Chan AT, Chang-Claude J, Chanock S, Conti DV, Curtis KR, Duggan D, Gallinger S, Gruber SB, Harrison TA, Hayes RB, Henderson BE, Hoffmeister M, Hopper JL, Hudson TJ, Hutter CM, Jackson RD, Jenkins MA, Kantor ED, Kolonel LN, Küry S, Le Marchand L, Lemire M, Newcomb PA, Potter JD, Qu C, Rosse SA, Schoen RE, Schumacher FR, Seminara D, Slattery ML, Ulrich CM, Zanke BW, Peters U. Genome-wide search for gene-gene interactions in colorectal cancer. *PLoS One* 2012; **7**: e52535 [PMID: 23300701 DOI: 10.1371/journal.pone.0052535]

176 **Dunlop MG**, Dobbins SE, Farrington SM, Jones AM, Palles C, Whiffin N, Tenesa A, Spain S, Broderick P, Ooi LY, Domingo E, Smillie C, Henrion M, Frampton M, Martin L, Grimes G, Gorman M, Semple C, Ma YP, Barclay E, Prendergast J, Cazier JB, Olver B, Penegar S, Lubbe S, Chander I, Carvajal-Carmona LG, Ballereau S, Lloyd A, Vijayakrishnan J, Zgaga L, Rudan I, Theodoratou E, Starr JM, Deary I, Kirac I, Kovacević D, Aaltonen LA, Renkonen-Sinisalo L, Mecklin JP, Matsuda K, Nakamura Y, Okada Y, Gallinger S, Duggan DJ, Conti D, Newcomb P, Hopper J, Jenkins MA, Schumacher F, Casey G, Easton D, Shah M, Pharoah P, Lindblom A, Liu T, Smith CG, West H, Cheadle JP, Midgley R, Kerr DJ, Campbell H, Tomlinson IP, Houlston RS. Common variation near CDKN1A, POLD3 and SHROOM2 influences colorectal cancer risk. *Nat Genet* 2012; **44**: 770-776 [PMID: 22634755 DOI: 10.1038/ng.2293]

177 **Tomlinson IP**, Webb E, Carvajal-Carmona L, Broderick P, Howarth K, Pittman AM, Spain S, Lubbe S, Walther A, Sullivan K, Jaeger E, Fielding S, Rowan A, Vijayakrishnan J, Domingo E, Chandler I, Kemp Z, Qureshi M, Farrington SM, Tenesa A, Prendergast JG, Barnetson RA, Penegar S, Barclay E, Wood W, Martin L, Gorman M, Thomas H, Peto J, Bishop DT, Gray R, Maher ER, Lucassen A, Kerr D, Evans DG, Schafmayer C, Buch S, Völzke H, Hampe J, Schreiber S, John U, Koessler T, Pharoah P, van Wezel T, Morreau H, Wijnen JT, Hopper JL, Southey MC, Giles GG, Severi G, Castellví-Bel S, Ruiz-Ponte C, Carracedo A, Castells A, Försti A, Hemminki K, Vodicka P, Naccarati A, Lipton L, Ho JW, Cheng KK, Sham PC, Luk J, Agúndez JA, Ladero JM, de la Hoya M, Caldés T, Niittymäki I, Tuupanen S, Karhu A, Aaltonen

L, Cazier JB, Campbell H, Dunlop MG, Houlston RS. A genome-wide association study identifies colorectal cancer susceptibility loci on chromosomes 10p14 and 8q23.3. *Nat Genet* 2008; **40**: 623-630 [PMID: 18372905 DOI: 10.1038/ng.111]

178 **Tomlinson I**, Webb E, Carvajal-Carmona L, Broderick P, Kemp Z, Spain S, Penegar S, Chandler I, Gorman M, Wood W, Barclay E, Lubbe S, Martin L, Sellick G, Jaeger E, Hubner R, Wild R, Rowan A, Fielding S, Howarth K, Silver A, Atkin W, Muir K, Logan R, Kerr D, Johnstone E, Sieber O, Gray R, Thomas H, Peto J, Cazier JB, Houlston R. A genome-wide association scan of tag SNPs identifies a susceptibility variant for colorectal cancer at 8q24.21. *Nat Genet* 2007; **39**: 984-988 [PMID: 17618284 DOI: 10.1038/ng2085]

179 **Zanke BW**, Greenwood CM, Rangrej J, Kustra R, Tenesa A, Farrington SM, Prendergast J, Olschwang S, Chiang T, Crowdy E, Ferretti V, Laflamme P, Sundararajan S, Roumy S, Olivier JF, Robidoux F, Sladek R, Montpetit A, Campbell P, Bezieau S, O'Shea AM, Zogopoulos G, Cotterchio M, Newcomb P, McLaughlin J, Younghusband B, Green R, Green J, Porteous ME, Campbell H, Blanche H, Sahbatou M, Tubacher E, Bonaiti-Pellié C, Buecher B, Riboli E, Kury S, Chanock SJ, Potter J, Thomas G, Gallinger S, Hudson TJ, Dunlop MG. Genome-wide association scan identifies a colorectal cancer susceptibility locus on chromosome 8q24. *Nat Genet* 2007; **39**: 989-994 [PMID: 17618283 DOI: 10.1038/ng2089]

180 **Tenesa A**, Farrington SM, Prendergast JG, Porteous ME, Walker M, Haq N, Barnetson RA, Theodoratou E, Cetnarskyj R, Cartwright N, Semple C, Clark AJ, Reid FJ, Smith LA, Kavoussanakis K, Koessler T, Pharoah PD, Buch S, Schafmayer C, Tepel J, Schreiber S, Völzke H, Schmidt CO, Hampe J, Chang-Claude J, Hoffmeister M, Brenner H, Wilkening S, Canzian F, Capella G, Moreno V, Deary IJ, Starr JM, Tomlinson IP, Kemp Z, Howarth K, Carvajal-Carmona L, Webb E, Broderick P, Vijayakrishnan J, Houlston RS, Rennert G, Ballinger D, Rozek L, Gruber SB, Matsuda K, Kidokoro T, Nakamura Y, Zanke BW, Greenwood CM, Rangrej J, Kustra R, Montpetit A, Hudson TJ, Gallinger S, Campbell H, Dunlop MG. Genome-wide association scan identifies a colorectal cancer susceptibility locus on 11q23 and replicates risk loci at 8q24 and 18q21. *Nat Genet* 2008; **40**: 631-637 [PMID: 18372901 DOI: 10.1038/ng.133]

181 **Peters U**, Hutter CM, Hsu L, Schumacher FR, Conti DV, Carlson CS, Edlund CK, Haile RW, Gallinger S, Zanke BW, Lemire M, Rangrej J, Vijayaraghavan R, Chan AT, Hazra A, Hunter DJ, Ma J, Fuchs CS, Giovannucci EL, Kraft P, Liu Y, Chen L, Jiao S, Makar KW, Taverna D, Gruber SB, Rennert G, Moreno V, Ulrich CM, Woods MO, Green RC, Parfrey PS, Prentice RL, Kooperberg C, Jackson RD, Lacroix AZ, Caan BJ, Hayes RB, Berndt SI, Chanock SJ, Schoen RE, Chang-Claude J, Hoffmeister M, Brenner H, Frank B, Bézieau S, Küry S, Slattery ML, Hopper JL, Jenkins MA, Le Marchand L, Lindor NM, Newcomb PA, Seminara D, Hudson TJ, Duggan DJ, Potter JD, Casey G. Meta-analysis of new genome-wide association studies of colorectal cancer risk. *Hum Genet* 2012; **131**: 217-234 [PMID: 21761138 DOI: 10.1007/s00439-011-1055-0]

182 **Houlston RS**, Webb E, Broderick P, Pittman AM, Di Bernardo MC, Lubbe S, Chandler I, Vijayakrishnan J, Sullivan K, Penegar S, Carvajal-Carmona L, Howarth K, Jaeger E, Spain SL, Walther A, Barclay E, Martin L, Gorman M, Domingo E, Teixeira AS, Kerr D, Cazier JB, Niittymäki I, Tuupanen S, Karhu A, Aaltonen LA, Tomlinson IP, Farrington SM, Tenesa A, Prendergast JG, Barnetson RA, Cetnarskyj R, Porteous ME, Pharoah PD, Koessler T, Hampe J, Buch S, Schafmayer C, Tepel J, Schreiber S, Völzke H, Chang-Claude J, Hoffmeister M, Brenner H, Zanke BW, Montpetit A, Hudson TJ, Gallinger S, Campbell H, Dunlop MG. Meta-analysis of genome-wide association data identifies four new susceptibility loci for colorectal cancer. *Nat Genet* 2008; **40**: 1426-1435 [PMID: 19011631 DOI: 10.1038/ng.262]

183 **Broderick P**, Carvajal-Carmona L, Pittman AM, Webb E, Howarth K, Rowan A, Lubbe S, Spain S, Sullivan K, Fielding S, Jaeger E, Vijayakrishnan J, Kemp Z, Gorman M, Chandler I, Papaemmanuil E, Penegar S, Wood W, Sellick G, Qureshi M, Teixeira A, Domingo E, Barclay E, Martin L, Sieber O, Kerr D, Gray R, Peto J, Cazier JB, Tomlinson I, Houlston RS. A genome-wide association study shows that common alleles of SMAD7 influence colorectal cancer risk. *Nat Genet* 2007; **39**: 1315-1317 [PMID: 17934461 DOI: 10.1038/ng.2007.18]

184 **Houlston RS**. COGENT (COlorectal cancer GENeTics) revisited. *Mutagenesis* 2012; **27**: 143-151 [PMID: 22294761 DOI: 10.1093/mutage/ger059]

185 **Hemminki K**, Försti A, Bermejo JL. The 'common disease-common variant' hypothesis and familial risks. *PLoS One* 2008; **3**: e2504 [PMID: 18560565 DOI: 10.1371/journal.pone.0002504]

186 **Hemminki K**, Försti A, Lorenzo Bermejo J. New cancer susceptibility loci: population and familial risks. *Int J Cancer* 2008; **123**: 1726-1729 [PMID: 18623115 DOI: 10.1002/ijc.23702]

187 **Middeldorp A**, Jagmohan-Changur S, van Eijk R, Tops C, Devilee P, Vasen HF, Hes FJ, Houlston R, Tomlinson I, Houwing-Duistermaat JJ, Wijnen JT, Morreau H, van Wezel T. Enrichment of low penetrance susceptibility loci in a Dutch familial colorectal cancer cohort. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 3062-3067 [PMID: 19843678 DOI: 10.1158/1055-9965.EPI-09-0601]

188 **Niittymäki I**, Kaasinen E, Tuupanen S, Karhu A, Järvinen H, Mecklin JP, Tomlinson IP, Di Bernardo MC, Houlston RS, Aaltonen LA. Low-penetrance susceptibility variants in familial colorectal cancer. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 1478-1483 [PMID: 20501757 DOI: 10.1158/1055-9965.EPI-09-1320]

189 **Ma X**, Zhang B, Zheng W. Genetic variants associated with colorectal cancer risk: comprehensive research synopsis, meta-analysis, and epidemiological evidence. *Gut* 2014; **63**: 326-336 [PMID: 23946381 DOI: 10.1136/gutjnl-2012-304121]

190 **Snover DC**. Update on the serrated pathway to colorectal carcinoma. *Hum Pathol* 2011; **42**: 1-10 [PMID: 20869746 DOI: 10.1016/j.humpath.2010.06.002]

191 **Kalady MF**, Jarrar A, Leach B, LaGuardia L, O'Malley M, Eng C, Church JM. Defining phenotypes and cancer risk in hyperplastic polyposis syndrome. *Dis Colon Rectum* 2011; **54**: 164-170 [PMID: 21228663 DOI: 10.1007/DCR.0b013e3181fd4c15]

192 **Carvajal-Carmona LG**, Howarth KM, Lockett M, Polanco-Echeverry GM, Volikos E, Gorman M, Barclay E, Martin L, Jones AM, Saunders B, Guenther T, Donaldson A, Paterson J, Frayling I, Novelli MR, Phillips R, Thomas HJ, Silver A, Atkin W, Tomlinson IP. Molecular classification and genetic pathways in hyperplastic polyposis syndrome. *J Pathol* 2007; **212**: 378-385 [PMID: 17503413 DOI: 10.1002/path.2187]

193 **Buchanan DD**, Sweet K, Drini M, Jenkins MA, Win AK, English DR, Walsh MD, Clendenning M, McKeone DM, Walters RJ, Roberts A, Pearson SA, Pavluk E, Hopper JL, Gattas MR, Goldblatt J, George J, Suthers GK, Phillips KD, Woodall S, Arnold J, Tucker K, Muir A, Field M, Greening S, Gallinger S, Perrier R, Baron JA, Potter JD, Haile R, Frankel W, de la Chapelle A, Macrae F, Rosty C, Walker NI, Parry S, Young JP. Risk factors for colorectal cancer in patients with multiple serrated polyps: a cross-sectional case series from genetics clinics. *PLoS One* 2010; **5**: e11636 [PMID: 20661287 DOI: 10.1371/journal.pone.0011636]

194 **Buchanan DD**, Sweet K, Drini M, Jenkins MA, Win AK, Gattas M, Walsh MD, Clendenning M, McKeone D, Walters R, Roberts A, Young A, Hampel H, Hopper JL, Goldblatt J, George J, Suthers GK, Phillips K, Young GP, Chow E, Parry S, Woodall S, Tucker K, Muir A, Field M, Greening S, Gallinger S, Green J, Woods MO, Spaetgens R, de la Chapelle A, Macrae F, Walker NI, Jass JR, Young JP. Phenotypic diversity

in patients with multiple serrated polyps: a genetics clinic study. *Int J Colorectal Dis* 2010; **25**: 703-712 [PMID: 20213458 DOI: 10.1007/s00384-010-0907-8]

195 **Ferrández A**, Samowitz W, DiSario JA, Burt RW. Phenotypic characteristics and risk of cancer development in hyperplastic polyposis: case series and literature review. *Am J Gastroenterol* 2004; **99**: 2012-2018 [PMID: 15447765 DOI: 10.1111/j.1572-0241.2004.30021.x]

196 **Lage P**, Cravo M, Sousa R, Chaves P, Salazar M, Fonseca R, Claro I, Suspiro A, Rodrigues P, Raposo H, Fidalgo P, Nobre-Leitão C. Management of Portuguese patients with hyperplastic polyposis and screening of at-risk first-degree relatives: a contribution for future guidelines based on a clinical study. *Am J Gastroenterol* 2004; **99**: 1779-1784 [PMID: 15330918 DOI: 10.1111/j.1572-0241.2004.30178.x]

197 **Chow E**, Lipton L, Lynch E, D'Souza R, Aragona C, Hodgkin L, Brown G, Winship I, Barker M, Buchanan D, Cowie S, Nasioulas S, du Sart D, Young J, Leggett B, Jass J, Macrae F. Hyperplastic polyposis syndrome: phenotypic presentations and the role of MBD4 and MYH. *Gastroenterology* 2006; **131**: 30-39 [PMID: 16831587 DOI: 10.1053/j.gastro.2006.03.046]

198 **Rubio CA**, Stemme S, Jaramillo E, Lindblom A. Hyperplastic polyposis coli syndrome and colorectal carcinoma. *Endoscopy* 2006; **38**: 266-270 [PMID: 16528654 DOI: 10.1055/s-2006-925026]

199 **Boparai KS**, Mathus-Vliegen EM, Koornstra JJ, Nagengast FM, van Leerdam M, van Noesel CJ, Houben M, Cats A, van Hest LP, Fockens P, Dekker E. Increased colorectal cancer risk during follow-up in patients with hyperplastic polyposis syndrome: a multicentre cohort study. *Gut* 2010; **59**: 1094-1100 [PMID: 19710031 DOI: 10.1136/gut.2009.185884]

200 **Win AK**, Walters RJ, Buchanan DD, Jenkins MA, Sweet K, Frankel WL, de la Chapelle A, McKeone DM, Walsh MD, Clendenning M, Pearson SA, Pavluk E, Nagler B, Hopper JL, Gattas MR, Goldblatt J, George J, Suthers GK, Phillips KD, Woodall S, Arnold J, Tucker K, Field M, Greening S, Gallinger S, Aronson M, Perrier R, Woods MO, Green JS, Walker N, Rosty C, Parry S, Young JP. Cancer risks for relatives of patients with serrated polyposis. *Am J Gastroenterol* 2012; **107**: 770-778 [PMID: 22525305 DOI: 10.1038/ajg.2012.52]

201 **Rosty C**, Hewett DG, Brown IS, Leggett BA, Whitehall VL. Serrated polyps of the large intestine: current understanding of diagnosis, pathogenesis, and clinical management. *J Gastroenterol* 2013; **48**: 287-302 [PMID: 23208018 DOI: 10.1007/s00535-012-0720-y]

202 **Rosty C**, Walsh MD, Walters RJ, Clendenning M, Pearson SA, Jenkins MA, Win AK, Hopper JL, Sweet K, Frankel WL, Aronson M, Gallinger S, Goldblatt J, Tucker K, Greening S, Gattas MR, Woodall S, Arnold J, Walker NI, Parry S, Young JP, Buchanan DD. Multiplicity and molecular heterogeneity of colorectal carcinomas in individuals with serrated polyposis. *Am J Surg Pathol* 2013; **37**: 434-442 [PMID: 23211288 DOI: 10.1097/PAS.0b013e318270f748]

203 **Young J**, Jass JR. The case for a genetic predisposition to serrated neoplasia in the colorectum: hypothesis and review of the literature. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 1778-1784 [PMID: 17035382 DOI: 10.1158/1055-9965.EPI-06-0164]

204 **Jasperson KW**, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. *Gastroenterology* 2010; **138**: 2044-2058 [PMID: 20420945 DOI: 10.1053/j.gastro.2010.01.054]

205 **Boparai KS**, Dekker E, Van Eeden S, Polak MM, Bartelsman JF, Mathus-Vliegen EM, Keller JJ, van Noesel CJ. Hyperplastic polyps and sessile serrated adenomas as a phenotypic expression of MYH-associated polyposis. *Gastroenterology* 2008; **135**: 2014-2018 [PMID: 19013464 DOI: 10.1053/j.gastro.2008.09.020]

206 **Cheah PY**. Recent advances in colorectal cancer genetics and diagnostics. *Crit Rev Oncol Hematol* 2009; **69**: 45-55 [PMID: 18774731 DOI: 10.1016/j.critrevonc.2008.08.001]

207 **Heald B**, Mester J, Rybicki L, Orloff MS, Burke CA, Eng C. Frequent gastrointestinal polyps and colorectal adenocarcinomas in a prospective series of PTEN mutation carriers. *Gastroenterology* 2010; **139**: 1927-1933 [PMID: 20600018 DOI: 10.1053/j.gastro.2010.06.061]

208 **Mongin C**, Coulet F, Lefevre JH, Colas C, Svrcek M, Eyries M, Lahely Y, Fléjou JF, Soubrier F, Parc Y. Unexplained polyposis: a challenge for geneticists, pathologists and gastroenterologists. *Clin Genet* 2012; **81**: 38-46 [PMID: 21476993 DOI: 10.1111/j.1399-0004.2011.01676.x]

209 **Clendenning M**, Young JP, Walsh MD, Woodall S, Arnold J, Jenkins M, Win AK, Hopper JL, Sweet K, Gallinger S, Rosty C, Parry S, Buchanan DD. Germline Mutations in the Polyposis-Associated Genes BMPR1A, SMAD4, PTEN, MUTYH and GREM1 Are Not Common in Individuals with Serrated Polyposis Syndrome. *PLoS One* 2013; **8**: e66705 [PMID: 23805267 DOI: 10.1371/journal.pone.0066705]

210 **Samowitz WS**, Albertsen H, Sweeney C, Herrick J, Caan BJ, Anderson KE, Wolff RK, Slattery ML. Association of smoking, CpG island methylator phenotype, and V600E BRAF mutations in colon cancer. *J Natl Cancer Inst* 2006; **98**: 1731-1738 [PMID: 17148775 DOI: 10.1093/jnci/djj468]

211 **Walker RG**, Landmann JK, Hewett DG, Worthley DL, Buttenshaw RL, Knight N, Webb PM, Whiteman DC, Whitehall VL, Leggett BA. Hyperplastic polyposis syndrome is associated with cigarette smoking, which may be a modifiable risk factor. *Am J Gastroenterol* 2010; **105**: 1642-1647 [PMID: 20125129 DOI: 10.1038/ajg.2009.757]

212 **Wallace K**, Grau MV, Ahnen D, Snover DC, Robertson DJ, Mahnke D, Gui J, Barry EL, Summers RW, McKeown-Eyssen G, Haile RW, Baron JA. The association of lifestyle and dietary factors with the risk for serrated polyps of the colorectum. *Cancer Epidemiol Biomarkers Prev* 2009; **18**: 2310-2317 [PMID: 19661090 DOI: 10.1158/1055-9965.EPI-09-0211]

213 **Lindor NM**, Rabe K, Petersen GM, Haile R, Casey G, Baron J, Gallinger S, Bapat B, Aronson M, Hopper J, Jass J, LeMarchand L, Grove J, Potter J, Newcomb P, Terdiman JP, Conrad P, Moslein G, Goldberg R, Ziogas A, Anton-Culver H, de Andrade M, Siegmund K, Thibodeau SN, Boardman LA, Seminara D. Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. *JAMA* 2005; **293**: 1979-1985 [PMID: 15855431 DOI: 10.1001/jama.293.16.1979]

214 **Llor X**, Pons E, Xicola RM, Castells A, Alenda C, Piñol V, Andreu M, Castellví-Bel S, Payá A, Jover R, Bessa X, Girós A, Roca A, Gassull MA. Differential features of colorectal cancers fulfilling Amsterdam criteria without involvement of the mutator pathway. *Clin Cancer Res* 2005; **11**: 7304-7310 [PMID: 16243801 DOI: 10.1158/1078-0432.CCR-05-0965]

215 **Mueller-Koch Y**, Vogelsang H, Kopp R, Lohse P, Keller G, Aust D, Muders M, Gross M, Daum J, Schiemann U, Grabowski M, Scholz M, Kerker B, Becker I, Henke G, Holinski-Feder E. Hereditary non-polyposis colorectal cancer: clinical and molecular evidence for a new entity of hereditary colorectal cancer. *Gut* 2005; **54**: 1733-1740 [PMID: 15955785 DOI: 10.1136/gut.2004.060905]

216 **Valle L**, Perea J, Carbonell P, Fernandez V, Dotor AM, Benitez J, Urioste M. Clinicopathologic and pedigree differences in amsterdam I-positive hereditary nonpolyposis colorectal cancer families according to tumor microsatellite instability status. *J Clin Oncol* 2007; **25**: 781-786 [PMID: 17228022 DOI: 10.1200/JCO.2006.06.9781]

217 **Francisco I**, Albuquerque C, Lage P, Belo H, Vitoriano I, Filipe B, Claro I, Ferreira S, Rodrigues P, Chaves P, Leitão CN, Pereira AD. Familial colorectal cancer type X syndrome: two distinct molecular entities? *Fam Cancer* 2011; **10**: 623-631 [PMID: 21837511 DOI: 10.1007/s10689-011-9473-7]

218 **Abdel-Rahman WM**, Ollikainen M, Kariola R, Järvinen HJ, Mecklin JP, Nyström-Lahti M, Knuutila S, Peltomäki P. Comprehensive characterization of HNPCC-related colorectal

cancers reveals striking molecular features in families with no germline mismatch repair gene mutations. *Oncogene* 2005; **24**: 1542-1551 [PMID: 15674332 DOI: 10.1038/sj.onc.1208387]

219 **Goel A**, Xicola RM, Nguyen TP, Doyle BJ, Sohn VR, Bandipalliam P, Rozek LS, Reyes J, Cordero C, Balaguer F, Castells A, Jover R, Andreu M, Syngal S, Boland CR, Llor X. Aberrant DNA methylation in hereditary nonpolyposis colorectal cancer without mismatch repair deficiency. *Gastroenterology* 2010; **138**: 1854-1862 [PMID: 20102720 DOI: 10.1053/j.gastro.2010.01.035]

220 **Middeldorp A**, van Eijk R, Oosting J, Forte GI, van Puijenbroek M, van Nieuwenhuizen M, Corver WE, Ruano D, Caldes T, Wijnen J, Morreau H, van Wezel T. Increased frequency of 20q gain and copy-neutral loss of heterozygosity in mismatch repair proficient familial colorectal carcinomas. *Int J Cancer* 2012; **130**: 837-846 [PMID: 21445971 DOI: 10.1002/ijc.26093]

221 **Therkildsen C**, Jönsson G, Dominguez-Valentin M, Nissen A, Rambech E, Halvarsson B, Bernstein I, Borg K, Nilbert M. Gain of chromosomal region 20q and loss of 18 discriminates between Lynch syndrome and familial colorectal cancer. *Eur J Cancer* 2013; **49**: 1226-1235 [PMID: 23245329 DOI: 10.1016/j.ejca.2012.11.011]

222 **Wiesner GL**, Daley D, Lewis S, Ticknor C, Platzer P, Lutterbaugh J, MacMillen M, Baliner B, Willis J, Elston RC, Markowitz SD. A subset of familial colorectal neoplasia kindreds linked to chromosome 9q22.2-31.2. *Proc Natl Acad Sci USA* 2003; **100**: 12961-12965 [PMID: 14566058 DOI: 10.1073/pnas.2132286100]

223 **Kemp ZE**, Carvajal-Carmona LG, Barclay E, Gorman M, Martin L, Wood W, Rowan A, Donohue C, Spain S, Jaeger E, Evans DG, Maher ER, Bishop T, Thomas H, Houlston R, Tomlinson I. Evidence of linkage to chromosome 9q22.33 in colorectal cancer kindreds from the United Kingdom. *Cancer Res* 2006; **66**: 5003-5006 [PMID: 16707420 DOI: 10.1158/0008-5472.CAN-05-4074]

224 **Skoglund J**, Djureinovic T, Zhou XL, Vandrovcova J, Renkonen E, Iselius L, Bisgaard ML, Peltomäki P, Lindblom A. Linkage analysis in a large Swedish family supports the presence of a susceptibility locus for adenoma and colorectal cancer on chromosome 9q22.32-31.1. *J Med Genet* 2006; **43**: e7 [PMID: 16467217 DOI: 10.1136/jmg.2005.033928]

225 **Gray-McGuire C**, Guda K, Adrianto I, Lin CP, Natale L, Potter JD, Newcomb P, Poole EM, Ulrich CM, Lindor N, Goode EL, Fridley BL, Jenkins R, Le Marchand L, Casey G, Haile R, Hopper J, Jenkins M, Young J, Buchanan D, Gallinger S, Adams M, Lewis S, Willis J, Elston R, Markowitz SD, Wiesner GL. Confirmation of linkage to and localization of familial colon cancer risk haplotype on chromosome 9q22. *Cancer Res* 2010; **70**: 5409-5418 [PMID: 20551049 DOI: 10.1158/0008-5472.CAN-10-0188]

226 **Neklason DW**, Kerber RA, Nilson DB, Anton-Culver H, Schwartz AG, Griffin CA, Lowery JT, Schildkraut JM, Evans JP, Tomlinson GE, Strong LC, Miller AR, Stopfer JE, Finkelstein DM, Nadkarni PM, Kasten CH, Mineau GP, Burt RW. Common familial colorectal cancer linked to chromosome 7q31: a genome-wide analysis. *Cancer Res* 2008; **68**: 8993-8997 [PMID: 18974144 DOI: 10.1158/0008-5472.CAN-08-1376]

227 **Papaemmanuil E**, Carvajal-Carmona L, Sellick GS, Kemp Z, Webb E, Spain S, Sullivan K, Barclay E, Lubbe S, Jaeger E, Vijayakrishnan J, Broderick P, Gorman M, Martin L, Lucassen A, Bishop DT, Evans DG, Maher ER, Steinke V, Rahner N, Schackert HK, Goecke TO, Holinski-Feder E, Propping P, Van Wezel T, Wijnen J, Cazier JB, Thomas H, Houlston RS, Tomlinson I. Deciphering the genetics of hereditary non-syndromic colorectal cancer. *Eur J Hum Genet* 2008; **16**: 1477-1486 [PMID: 18628789 DOI: 10.1038/ejhg.2008.129]

228 **Picelli S**, Vandrovcova J, Jones S, Djureinovic T, Skoglund J, Zhou XL, Velculescu VE, Vogelstein B, Lindblom A. Genome-wide linkage scan for colorectal cancer susceptibility genes supports linkage to chromosome 3q. *BMC Cancer* 2008; **8**: 87 [PMID: 18380902 DOI: 10.1186/1471-2407-8-87]

229 **Neklason DW**, Tuohy TM, Stevens J, Otterud B, Baird L, Kerber RA, Samowitz WS, Kuwada SK, Leppert MF, Burt RW. Colorectal adenomas and cancer link to chromosome 13q22.1-13q31.3 in a large family with excess colorectal cancer. *J Med Genet* 2010; **47**: 692-699 [PMID: 20522424 DOI: 10.1136/jmg.2009.076091]

230 **Saunders IW**, Ross J, Macrae F, Young GP, Blanco I, Brohede J, Brown G, Brookes D, Lockett T, Molloy PL, Moreno V, Capella G, Hannan GN. Evidence of linkage to chromosomes 10p15.3-p15.1, 14q24.3-q31.1 and 9q33.3-q34.3 in non-syndromic colorectal cancer families. *Eur J Hum Genet* 2012; **20**: 91-96 [PMID: 21829229 DOI: 10.1038/ejhg.2011.149]

231 **Jones S**, Hruban RH, Kamiyama M, Borges M, Zhang X, Parsons DW, Lin JC, Palmisano E, Brune K, Jaffee EM, Iacobuzio-Donahue CA, Maitra A, Parmigiani G, Kern SE, Velculescu VE, Kinzler KW, Vogelstein B, Eshleman JR, Goggins M, Klein AP. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. *Science* 2009; **324**: 217 [PMID: 19264984 DOI: 10.1126/science.1171202]

232 **Comino-Méndez I**, Gracia-Aznárez FJ, Schiavi F, Landa I, Leandro-García LJ, Letón R, Honrado E, Ramos-Medina R, Caronia D, Pita G, Gómez-Graña A, de Cubas AA, Inglada-Pérez L, Maliszewska A, Taschin E, Bobisse S, Pica G, Loli P, Hernández-Lavado R, Díaz JA, Gómez-Morales M, González-Neira A, Roncador G, Rodríguez-Antona C, Benítez J, Mannelli M, Opocher G, Robledo M, Cascón A. Exome sequencing identifies MAX mutations as a cause of hereditary pheochromocytoma. *Nat Genet* 2011; **43**: 663-667 [PMID: 21685915 DOI: 10.1038/ng.861]

233 **Kim JC**, Roh SA, Yoon YS, Kim HC, Park IJ. MLH3 and EXO1 alterations in familial colorectal cancer patients not fulfilling Amsterdam criteria. *Cancer Genet Cytogenet* 2007; **176**: 172-174 [PMID: 17656264 DOI: 10.1016/j.cancergencyto.2007.04.011]

234 **Gylfe AE**, Sirkiä J, Ahlsten M, Järvinen H, Mecklin JP, Karhu A, Aaltonen LA. Somatic mutations and germline sequence variants in patients with familial colorectal cancer. *Int J Cancer* 2010; **127**: 2974-2980 [PMID: 21351276 DOI: 10.1002/ijc.25529]

235 **Coissieux MM**, Tomsic J, Castets M, Hampel H, Tuupanen S, Andrieu N, Comeras I, Drouet Y, Lasset C, Liyanarachchi S, Mazelin L, Puisieux A, Saurin JC, Scoazec JY, Wang Q, Aaltonen L, Tanner SM, de la Chapelle A, Bernet A, Mehlen P. Variants in the netrin-1 receptor UNC5C prevent apoptosis and increase risk of familial colorectal cancer. *Gastroenterology* 2011; **141**: 2039-2046 [PMID: 21893118 DOI: 10.1053/j.gastro.2011.08.041]

236 **Garre P**, Briceño V, Xicola RM, Doyle BJ, de la Hoya M, Sanz J, Llovet P, Pescador P, Puente J, Díaz-Rubio E, Llor X, Caldés T. Analysis of the oxidative damage repair genes NUDT1, OGG1, and MUTYH in patients from mismatch repair proficient HNPCC families (MSS-HNPCC). *Clin Cancer Res* 2011; **17**: 1701-1712 [PMID: 21355073 DOI: 10.1158/1078-0432.CCR-10-2491]

237 **de Voer RM**, Geurts van Kessel A, Weren RD, Ligtenberg MJ, Smeets D, Fu L, Vreede L, Kamping EJ, Verwiel ET, Hahn MM, Ariaans M, Spruijt L, van Essen T, Houge G, Schackert HK, Sheng JQ, Venselaar H, van Ravenswaaij-Arts CM, van Krieken JH, Hoogerbrugge N, Kuiper RP. Germline mutations in the spindle assembly checkpoint genes BUB1 and BUB3 are risk factors for colorectal cancer. *Gastroenterology* 2013; **145**: 544-547 [PMID: 23747338 DOI: 10.1053/j.gastro.2013.06.001]

238 **Ku CS**, Cooper DN, Wu M, Roukos DH, Pawitan Y, Soong R, Iacopetta B. Gene discovery in familial cancer syndromes by exome sequencing: prospects for the elucidation of familial colorectal cancer type X. *Mod Pathol* 2012; **25**: 1055-1068 [PMID: 22522846 DOI: 10.1038/modpathol.2012.62]

239 **Middeldorp A**, Jagmohan-Changur SC, van der Klift HM, van Puijenbroek M, Houwing-Duistermaat JJ, Webb E, Houlston R, Tops C, Vasen HF, Devilee P, Morreau H, van Wezel T, Wijnen J. Comprehensive genetic analysis of seven large families with mismatch repair proficient colorectal cancer. *Genes Chromosomes Cancer* 2010; **49**: 539-548 [PMID: 20222047]

240 **Nejentsev S**, Walker N, Riches D, Egholm M, Todd JA. Rare variants of IFIH1, a gene implicated in antiviral responses, protect against type 1 diabetes. *Science* 2009; **324**: 387-389 [PMID: 19264985 DOI: 10.1126/science.1167728]

241 **Johansen CT**, Wang J, Lanktree MB, Cao H, McIntyre AD, Ban MR, Martins RA, Kennedy BA, Hassell RG, Visser ME, Schwartz SM, Voight BF, Elosua R, Salomaa V, O'Donnell CJ, Dallinga-Thie GM, Anand SS, Yusuf S, Huff MW, Kathiresan S, Hegele RA. Excess of rare variants in genes identified by genome-wide association study of hypertriglyceridemia. *Nat Genet* 2010; **42**: 684-687 [PMID: 20657596]

242 **Momozawa Y**, Mni M, Nakamura K, Coppieters W, Almer S, Amininejad L, Cleynen I, Colombel JF, de Rijk P, Dewit O, Finkel Y, Gassull MA, Goossens D, Laukens D, Lémann M, Libioulle C, O'Morain C, Reenaers C, Rutgeerts P, Tysk C, Zelenika D, Lathrop M, Del-Favero J, Hugot JP, de Vos M, Franchimont D, Vermeire S, Louis E, Georges M. Resequencing of positional candidates identifies low frequency IL23R coding variants protecting against inflammatory bowel disease. *Nat Genet* 2011; **43**: 43-47 [PMID: 21151126 DOI: 10.1038/ng.733]

243 **Rivas MA**, Beaudoin M, Gardet A, Stevens C, Sharma Y, Zhang CK, Boucher G, Ripke S, Ellinghaus D, Burtt N, Fennell T, Kirby A, Latiano A, Goyette P, Green T, Halfvarson J, Haritunians T, Korn JM, Kuruvilla F, Lagacé C, Neale B, Lo KS, Schumm P, Törkvist L, Dubinsky MC, Brant SR, Silverberg MS, Duerr RH, Altshuler D, Gabriel S, Lettre G, Franke A, D'Amato M, McGovern DP, Cho JH, Rioux JD, Xavier RJ, Daly MJ. Deep resequencing of GWAS loci identifies independent rare variants associated with inflammatory bowel disease. *Nat Genet* 2011; **43**: 1066-1073 [PMID: 21983784]

P- Reviewer: Elpek GO, Lu F, Serafino A **S- Editor**: Gou SX
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ISSN 1007-9327