Update on genetic predisposition to colorectal cancer and polyposis

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ABSTRACT

The present article summarizes recent developments in the characterization of genetic predisposition to colorectal cancer (CRC). The main themes covered include new hereditary CRC and polyposis syndromes, non-CRC hereditary cancer genes found mutated in CRC patients, strategies used to identify novel causal genes, and review of candidate genes that have been proposed to predispose to CRC and/or colonic polyposis. We provide an overview of newly described genes and syndromes associated with predisposition to CRC and polyposis, including: polymerase proofreading-associated polyposis, *NTHL1*-associated polyposis, mismatch repair gene biallelic inactivation-related adenomatous polyposis (including *MSH3*- and *MLH3*-associated polyposes), *GREM1*-associated mixed polyposis, *RNF43*-associated serrated polyposis, and *RPS20* mutations as a rare cause of hereditary nonpolyposis CRC. The implementation of next generation sequencing approaches for genetic testing has exposed the presence of pathogenic germline variants in genes associated with hereditary cancer syndromes not traditionally linked to CRC, which may have an impact on genetic testing, counseling and surveillance. The identification of new hereditary CRC and polyposis genes has not deemed an easy endeavor, even though known CRC-related genes explain a small proportion of the estimated familial risk. Whole-genome sequencing may offer a technology for increasing this proportion, particularly if applied on pedigree data allowing linkage type of analysis. The final section critically surveys the large number of candidate genes that have been recently proposed for CRC predisposition.

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1. Introduction

Genetic predisposition, due to pathogenic germline variants in high risk cancer genes, has been implicated in 2–8% of all CRCs (and 1 in 5 of those diagnosed at age < 50) (AlDubayan et al., 2018; DeRycke et al., 2017; Mork et al., 2015; Pearlman et al., 2017; Stoffel et al., 2018; Yurgelun et al., 2017). This genetic predisposition to CRC has been classically associated with germline mutations or epimutations in the DNA mismatch repair (MMR) genes *MLH1, MSH2, MSH6* and *PMS2* for nonpolyposis cases, and in *APC* and *MUTYH* (recessive inheritance) for adenomatous colonic polyposis. Other -less frequent- CRC predisposing syndromes, characterized by the presence of hamartomatous polyps, are caused by mutations in *SMAD4, BMPR1A, STK11* and *PTEN* (Valle, 2014). Despite this knowledge, much of the genetic predisposition to CRC and polyposis is still unexplained. In the last years, important efforts have been invested to identify new causal genes that explain this predisposition, as the identification of a germline pathogenic mutation that causes the increased risk and aggregation of CRC in a family has clear consequences in the clinical management of its members. The following article provides an overview of the newly identified genes and syndromes associated with predisposition to CRC and polyposis, and assesses the involvement of *a priori* non-CRC hereditary cancer genes in CRC predisposition. Likewise, recent and efficient tools for causal gene identification are surveyed, and a final section reviews the candidate genes proposed in the last years.

2. New hereditary colorectal cancer (CRC) and polyposis syndromes

2.1. Polymerase proofreading-associated polyposis

The evolution of a normal cell into a cancerous cell has been regarded for long as a result of multiple changes in nucleic acids sequences, chromosomal rearrangements and aneuploidy. This genome instability permits to acquire biological capacities such as sustaining proliferative signaling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing angiogenesis, and activating invasion and metastasis (Hanahan and Weinberg, 2011). Alterations in replicative DNA polymerases increase the rate of base pairing errors and contribute to this instability. In eukaryote cells, high-fidelity DNA replication is accomplished by three DNA polymerases, POL alfa, POL epsilon and POL delta (Lujan et al., 2016), and post-replicative mismatch repair (MMR) (Kunkel, 2004). MMR germline defects have been known for 25 years to be one of the causes of genetic predisposition to CRC (Fishel et al., 1993), whereas pathogenic variants affecting the proofreading activity of DNA replicative polymerases were very

recently associated with hereditary cancers (Palles et al., 2013).

POLE and POLD1 belong to the B family of replicative and repair DNA polymerases. In DNA replication, they act as the major catalytic and proofreading subunits of the POL epsilon and POL delta complexes, respectively synthesizing the leading and lagging DNA strands (Nick McElhinny et al., 2008). They have a proofreading function, performed by their exonuclease domain, which detects and removes misincorporated bases in the daughter strand through failed complementary pairing with the parental strand (Miyabe et al., 2011). A ternary structure of the catalytic core of POLE and POLD1 from *Saccharomyces cerevisiae* in complex with DNA and an incoming nucleotide were recently solved (Hogg et al., 2014; Swan et al., 2009). These structures can provide information about the selection of the correct nucleotide and the positions of amino acids that might be critical for proofreading activity and, therefore, it can be used to recognize potentially pathogenic genetic variants.

Germline pathogenic variants in human *POLE* and *POLD1* exonuclease domains have recently been reported to predispose to polymerase proofreading-associated polyposis (PPAP) (MIM# 615083 and 612591). This disease is characterized by multiple colorectal adenomas and carcinomas following an autosomal dominant pattern of inheritance and suspected high penetrance. *POLE* p.Leu424Val and *POLD1* p.Ser478Asn were the first two variants found by performing whole-genome sequencing in a small number of families with multiple polyposis and CRC and then replicated detecting additional carriers by genotyping 3,085 individuals from the UK with CRC (Palles et al., 2013). This leading work prompted the directed screening of both genes in subsequent familial CRC cohorts (Table 1).

Regarding associated phenotypes, pathogenic germline variants in *POLE* and *POLD1* were initially implicated in genetic predisposition to multiple polyposis and CRC (Palles et al., 2013). Later on, the phenotypic spectrum broadened to include other neoplasms such as endometrial cancer (Church et al., 2013), ovarian and brain tumors (Rohlin et al., 2014), pancreatic and small intestine cancer (Hansen et al., 2015), melanoma (Aoude et al., 2015) or a clinical phenotype suggestive of constitutional MMR deficiency (CMMRD) (Wimmer et al., 2017). With regard to the clinical management of exonuclease mutation carriers, Bellido et al. first proposed preliminary surveillance guidelines based on the overlapping phenotype of this syndrome with attenuated adenomatous polyposis (*APC/MUTYH*) and Lynch syndrome. The authors adapted the Amsterdam and Bethesda criteria to the attenuated polyposis scenario, taking into consideration additional specific *POLE/POLD1* characteristics such as the risk to endometrial cancer (Bellido et al., 2016). In 2018, Buchanan et al., after estimating CRC risks for POLE mutation carriers, recommended annual colonoscopy screening and clinical management guidelines comparable to those currently

Table 1
Studies screening *POLE* and *POLD1* among familial CRC cohorts.

POLE/POLD1 variants	Study group	Study methods	References
POLE p.Leu424Val; *POLD1* p.Leu474Pro	858 cases with familial and early-onset CRC or polyposis	Direct genotyping or Sanger sequencing of *POLE/POLD1*	Valle et al. (2014)
POLE p.Asn363Lys	1 large Swedish family with CRC and extra-intestinal tumors	WES	Rohlin et al. (2014)
POLE p.Leu424Val	266 unrelated German patients with polyposis or familial CRC	Targeted sequencing of *POLD1, POLD2, POLD3, POLD4, POLE, POLE2, POLE3* and *POLE4*	Spier et al. (2015)
POLE p.Tyr458Phe	1 large Norwegian family with colorectal adenomas and CRC, and extra-colonic cancers	WES	Hansen et al. (2015)
POLE p.Leu424Val; *POLD1* p.Asp316His, p.Asp316Gly, p.Arg409Trp, p.Leu474Pro	441 nonpolyposis familial CRC and 88 polyposis cases	Pooled DNA amplification and *POLE/POLD1* targeted sequencing	Bellido et al. (2016)
POLE p.Trp347Cys	34 melanoma families	WES	Aoude et al. (2015)
POLE p.Lys425Arg	76 patients with CRC and/or polyposis	Sanger Sequencing of *POLE*	Rohlin et al. (2016)
POLE p.Val411Leu	14-year-old patient with polyposis and CRC	Sanger sequencing of *POLE/POLD1*	Wimmer et al. (2017)
POLE p.Val474Ile	155 patients with multiple polyps or early-onset CRC phenotype	Sanger sequencing of *POLE/POLD1*	Esteban-Jurado et al. (2017)
POLE p.Asp275Val	274 Norwegian and Australian familial CRC	Multi-gene panel	Hansen et al. (2017)

Abbreviations: CRC, colorectal cancer; WES, whole-exome sequencing.

recommended for Lynch syndrome or familial adenomatous polyposis (Buchanan et al., 2018).

Outside cancer predisposition, pathogenic germline variants in *POLE* (homozygous c.4444+3A > G, skipping of exon 34) have also been involved in autosomal recessive predisposition to FILS syndrome, characterized by mild facial dysmorphism, mainly malar hypoplasia, livedo on the skin since birth, immunodeficiency resulting in recurrent infections, and short stature (Pachlopnik Schmid et al., 2012). Additionally, a pathogenic germline variant in *POLD1*, c.1812_1814delCT (p.Ser605del), has been linked in an autosomal dominant manner to germline predisposition to a multisystem disorder that includes subcutaneous lipodystrophy, deafness, mandibular hypoplasia and hypogonadism in males (Weedon et al., 2013), and also to Werner syndrome (heterozygous c.1812_1814delCTC (p.Ser605del) and c.1519C > T (p.R507C)) (Lessel et al., 2015). The non-cancerous phenotypes are caused by different variants than those leading to cancer.

As previously mentioned, high-fidelity DNA replication is accomplished by DNA polymerases, including POLE and POLD1, and post-replicative MMR. Indeed, POLD1 participates in the MMR system (Longley et al., 1997). These two systems have been recently linked regarding germline predisposition to CRC. The first *POLE* and *POLD1* alterations in human disease were precisely detected in MMR-defective CRC cell lines and tumors (Yoshida et al., 2011), implying that defective polymerase proofreading in concert with MMR deficiency could contribute to a cancer mutator phenotype. More recently, this relationship has been exemplified by the detection of concomitant germline *POLE* pathogenic variant and MMR somatic alterations in suggestive Lynch syndrome cases with loss of expression of MMR proteins (Elsayed et al., 2015; Jansen et al., 2016).

Besides their contribution to hereditary CRC, *POLE* and *POLD1* can also be somatically mutated. Tumor pathogenic variants in the *POLE* exonuclease domain have been identified in 1–2% of sporadic CRC and in 7–12% of endometrial cancers, as well as in tumors of the brain, pancreas, ovary, breast, stomach and uterus (Cancer Genome Atlas Network, 2012; Church et al., 2013). The most common somatic *POLE* variants are p.Pro286Arg and p.Val411Leu, but p.Ser297Phe, p.Ala456Pro and p.Ser459Phe have also been detected. On the other hand, somatic *POLD1* pathogenic variants seem to be much unusual in CRC. Regarding their timing in oncogenesis, *POLE* pathogenic variants are detectable in non-malignant precursor lesions of endometrial and CRC, indicating that they are early, quite possibly initiating, events (Temko et al., 2018). Carrying an alteration in replicative DNA polymerases increases the rate of base pairing errors. This fact is displayed in the tumors of germline and sporadic *POLE* mutated carriers as an ultramutated signature. This profile mainly involves base substitutions and not copy-number alterations, and produces a 100-fold increase in C-to-A transversions in the context of TCT and a 30-fold increase in C-to-T transitions in the context TCG (Alexandrov et al., 2013). The tumor mutational profile for *POLD1* alterations is believed to also involve ultramutation but is currently unknown. Cancer immunotherapy attempts to stimulate the immune system to destroy tumors by using immune checkpoint inhibitors that target immunosuppressive molecules such as PD1 and PDL1. High tumor mutation burden is a predictive marker for immunotherapy response. Hypermutated tumors show higher neo-antigen load and higher immunogenicity (Giannakis et al., 2016). MMR deficient, microsatellite-unstable and *POLE*-mutated tumors are good responders and show excellent prognosis (Domingo et al., 2016).

Finally, it is important to highlight the need to correctly assess the functional impact of *POLE* and *POLD1* genetic variants. Nowadays, next-generation sequencing projects easily identify genetic variation but it is extremely important to distinguish among causative, non-polymorphic germline variants, and somatic pathogenic, non-passenger variants with prognosis meaning. Several efforts have already characterized the functional effect of *POLE* variants in human cell-free assays (Shinbrot et al., 2014) and yeast (Barbari et al., 2018).

2.2. NTHL1-associated polyposis

After the identification of dominant germline pathogenic mutations in the adenomatous polyposis coli gene (*APC*) as a cause for familial adenomatous polyposis (MIM# 175100), many studies aimed to identify additional novel high-penetrant genes as cause for polyposis. The subsequent identification of recessive pathogenic variants in *MUTYH* as cause for polyposis and CRC (MIM# 608456), put the base-excision repair (BER) pathway in the spotlight for a role in cancer predisposition (Al-Tassan et al., 2002). Several studies performed candidate gene approaches to assess the occurrence of variants in multiple genes involved in the BER in polyposis and CRC (Broderick et al., 2006; Dallosso et al., 2008; Mur et al., 2018b; Smith et al., 2013b), but besides the identification of *MUTYH*, none of the other BER genes revealed a clear role in polyposis and CRC. However, in a recent whole-exome sequencing (WES) study, in which a stringently selected cohort of 51 cases who developed multiple adenomatous polyps at an early age in life were investigated, led to the identification of *NTHL1*, another BER gene, as a predisposing gene for polyposis and CRC (MIM# 616415) (Weren et al., 2015a). WES revealed that four individuals from three independent families carried a homozygous nonsense variant in *NTHL1* in their germline. Subsequent analyses of family members revealed complete co-segregation with the adenomatous polyposis phenotype. Moreover, six of the seven carriers of biallelic germline *NTHL1* pathogenic variants developed (multiple) tumors, including CRC and endometrial cancer (Weren et al., 2015a).

Since its discovery, several additional cases with biallelic germline mutations in *NTHL1* have been published (Belhadj et al., 2017; Broderick et al., 2017; Fostira et al., 2018; Rivera et al., 2015). In a very recent international study, 11 additional families with biallelic germline *NTHL1* nonsense variants are described (Grolleman et al., 2019). Whereas the initial families all carried a homozygous nonsense variant, p.Gln90*, recent literature also revealed cases with compound heterozygous pathogenic variants (all variants caused protein truncation of NTHL1). Collectively, up to now 32 cases from 20 families with NTHL1 deficiency have been reported. All patients that underwent a colonoscopy thus far (28 out of 32 cases) are described to have developed adenomatous polyposis and CRC, albeit that this may be the cause of inclusion bias. In addition, the majority of cases also presented with multiple extracolonic malignancies (Belhadj et al., 2017; Broderick et al., 2017; Fostira et al., 2018; Grolleman et al., 2019; Rivera et al., 2015; Weren et al., 2015a). Together, these data confirm that deficiency of NTHL1 causes polyposis and CRC, but also a tumor phenotype that is different (14 different tumor types reported so far) than what is known for *MUTYH*-associated polyposis (Win et al., 2016), including high risk of breast cancer (Grolleman et al., 2019). Grolleman et al. suggested that the established surveillance guidelines for MAP should be extended to biallelic *NTHL1* mutation carriers, starting colonoscopies at 18–20 years of age. Furthermore, breast cancer screening, based on moderate risk, is advised. For the other cancers no surveillance advices are currently described, due to uncertain cumulative cancer risks and/or adequate screening methods. However, endometrial cancer screening comparable with Lynch syndrome could be considered (Grolleman et al., 2019). Additional studies are needed to determine more precise cancer risk estimates and subsequently surveillance guidelines for biallelic *NTHL1* mutation carriers. Previous literature suggested the prevalence of *MUTYH*-associated polyposis to be 1:5,000–40,000 (Aretz et al., 2013). Recently, Weren et al. (2018) estimated the incidence of *MUTYH*-associated polyposis to be 1:19,079 in European individuals, based on the publically available Exome Aggregation Consortium (ExAC) database. Similarly, Weren et al. estimated that, based on protein truncation alleles of *NTHL1* in the ExAC database, the prevalence of *NTHL1*-associated tumor syndrome in the European population to be 1:114,770 (Weren et al., 2018). This data indicates that *NTHL1*-associated tumor syndrome is at least five times as rare as *MUTYH*-associated polyposis. The prevalence of pathogenic

alleles in *NTHL1*, such as the p.Gln90* allele, may vary between populations, which may explain why pathogenic variants in *NTHL1* were not identified previously (Broderick et al., 2006; Dallosso et al., 2008; Smith et al., 2013b; Viel et al., 2017).

The BER machinery is involved in the repair of base lesions, which can be caused by oxidative damage, alkylation or deamination. Tumors derived from *MUTYH*-associated polyposis patients have revealed somatic variants that have a strong bias towards C > A transversions. Mutational signature analyses (reviewed in more detail in chapter 6) has shown that C > A transversions caused by deficiency of MUTYH occur mainly in a NpCpA or NpCpT context (Pilati et al., 2017; Viel et al., 2017). Tumors derived from patients with *NTHL1*-associated tumor syndrome revealed a strong bias towards C > T transitions (Rivera et al., 2015; Weren et al., 2015a). A study in which *NTHL1* was knocked out in human intestinal organoids revealed that these C > T transitions mainly occur in a non-CpG context and that NTHL1 deficiency is the mutational process underlying signature 30 (Drost et al., 2017). By sequencing of CRCs and multiple extracolonic tumors from carriers of biallelic germline *NTHL1* pathogenic variants, Grolleman et al. showed that the absence of functional NTHL1 has likely driven formation of tumors in these patients, thereby confirming that deficiency of NTHL1 causes a multi tumor predisposition syndrome (Grolleman et al., 2019).

Signature 30 was originally identified in single breast cancer sample that, upon retrospective analysis of the sequencing data, revealed a heterozygous nonsense variant in *NTHL1* in the germline and subsequent NTHL1 deficiency in the breast cancer due to somatic loss of the wild-type *NTHL1* allele (Drost et al., 2017; Nik-Zainal et al., 2016). Whether carriers of a heterozygous germline *NTHL1* pathogenic variant have an increased cancer risk, like has been observed for monoallelic *MUTYH* carriers (Win et al., 2011), remains to be elucidated once more mutation carriers have been identified.

2.3. Germline biallelic inactivation of MMR genes as cause of adenomatous polyposis

Biallelic germline pathogenic variants in four MMR genes, *MLH1*, *MSH2*, *MSH6*, and *PMS2*, result in a rare, inherited cancer predisposition syndrome named constitutional MMR deficiency syndrome (CMMRD, MIM#276300). Individuals with CMMRD have a high risk of developing a diverse spectrum of malignancies already in childhood and adolescence. Approximately 80% of patients develop their first malignancy before the age of 18 years. The spectrum includes mainly T-cell non-Hodgkin lymphomas, high-grade gliomas and gastrointestinal, mainly colorectal tumors. The majority of the CMMRD patients show features typical of neurofibromatosis type I (NF1), particularly multiple café au lait spots (Bakry et al., 2014; Wimmer and Etzler, 2008).

Remarkably, a large proportion of CMMRD patients develop multiple synchronous adenomas ranging from a few up to > 100 polyps, mimicking attenuated familial adenomatous polyposis (Aronson et al., 2016; Jasperson et al., 2011; Levi et al., 2015; Toledano et al., 2009). Adenomas of the colon and rectum were reported in 52 (36%) of the patients, with a median age of 14 (range of first diagnosis between 6 and 46) (Wimmer et al., 2014). Most (35/52) of them showed high-grade dysplasia or had synchronous bowel cancer (Wimmer et al., 2014). Polyps in CMMRD can also resemble histologically to juvenile polyposis (Levi et al., 2015). Gastrointestinal manifestations are highly dependent on age of examination. All patients will have polyposis by the third decade of life (Aronson et al., 2016).

Duodenal adenomas are found in 5% of CMMR-D cases, carcinoma of the duodenal papilla, and gastric polyps have also been reported (Herkert et al., 2011; Levi et al., 2015; Wimmer et al., 2014). Therefore, as recommended by the care for MMRD consortium, CMMRD syndrome should be considered as a differential diagnosis in patients under the age of 25 years with multiple adenomas and absence of an *APC/MUTYH* pathogenic variant and/or one adenoma with high-grade dysplasia

under the age of 25 (Wimmer et al., 2014). Genetic testing for the presence of biallelic mutations in one of the four MMR genes is recommended to genetically confirm the diagnosis of CMMRD. When gene testing is not possible or yields unclear results, other tests, such as immunohistochemistry (IHC) revealing loss of the corresponding MMR proteins or MSI can be used. Due to reports of colonic polyps as early as 6 years of age, guidelines recommend ileo-colonoscopies, upper endoscopy and video capsule endoscopy (VCE), at least yearly from a young age, starting annual colonoscopies at 4–8 years, and small bowel surveillance from age 8–10 years (Durno et al., 2017; Tabori et al., 2017; Vasen et al., 2014). Preventive colectomy is recommended on the basis of the degree of dysplasia and numbers of polyps observed during endoscopies (Tabori et al., 2017).

In 2016, Adam et al. reported the presence of biallelic pathogenic variants in **MSH3**, an MMR gene not associated with Lynch syndrome, in adenomatous polyposis patients without mutations in known polyposis predisposing genes. The associated phenotype was characterized by the presence of colorectal adenomatous polyposis, diagnosed at their thirties in most cases, accompanied by additional benign and malignant lesions in the gastrointestinal tract and extracolonic. The phenotype observed in *MSH3* biallelic carriers largely resemble that of attenuated familial adenomatous polyposis, although still conserving some features of CMMRD occurring at more advanced age (not in the childhood) (Adam et al., 2016).

Similar to *MSH3*, a recent publication by Olkinuora et al. showed that a biallelic **MLH3** truncating variant, c.3563C > G (p.Ser1188*), founder in the studied Finnish population, causes classical or attenuated adenomatous polyposis and possibly extracolonic tumors, including breast cancer (Olkinuora et al., 2018).

2.4. GREM1-associated mixed polyposis

Hereditary mixed polyposis syndrome (HMPS1; MIM# 601228) originally was described in an large Ashkenazi Jewish (AJ) family whose members had multiple polyps of more than 1 histologic type (adenomas, hyperplastic, and juvenile), and/or individual polyps with overlapping histologic features (atypical juvenile with admixed histologic features) (Jaeger et al., 2012; Rozen et al., 2003; Thomas et al., 1996; Whitelaw et al., 1997). The underlying cause was a 40-kb duplication upstream of *GREM1* at chromosome 15:30,752,231–30,792,051 (hg19), associated with an increased allele-specific ectopic expression of GREM1 in the colon mucosa (Jaeger et al., 2012). Overexpression of GREM1 suppresses BMP (Jaeger et al., 2012), allowing epithelial cells retain stem cell-like properties, form ectopic crypts and ultimately become neoplastic (Davis et al., 2015) Additional reported cases of *GREM1* duplications include a family with a 16-kb duplication in the regulatory region (Rohlin et al., 2016), a patient with polyps and family history of CRC who carried a 24 kb duplication of the 5′ regulatory region (McKenna et al., 2019), a patient with early onset CRC with a large duplication encompassing the entire *GREM1* gene (Lieberman et al., 2012) and more AJ families with the 40-kb duplication (Davis et al., 2015; Laitman et al., 2015; Lieberman et al., 2017). The 40-kb duplication has been detected among 1:184 AJ with personal or family history of polyposis or CRC (Lieberman et al., 2017).

Polyposis is the prominent feature in HMPS1. In most HMPS1 families, ages at onset of polyps are in the late 20s or older, however, polyps at ages of 10, 16, and 18 have also been reported. Overlap of *GREM1* associated HMPS, familial adenomatous polyposis (FAP) and Lynch syndrome, and extracolonic tumors have been reported (Lieberman et al., 2017). Given the paucity of published descriptions of *GREM1*-associated HMPS, management of affected families is challenging. Current National Comprehensive Cancer Network recommendations for *GREM1* carriers are to begin colonoscopies at ages 25–30, repeated at 2- to 3-year intervals (1–2 years if polyps are detected) (NCCN, 2017). However, reports of polyp onset in the adolescence and rapid polyp progression to carcinoma (Lieberman et al., 2017; Rozen

et al., 2003), suggest earlier colonoscopy screening initiation.

Though the *GREM1* 5′ regulatory region is now analyzed on many different multi-gene cancer panels, CNVs of regulatory regions are not typically analyzed in NGS data, thus, could be easily missed.

2.5. RNF43-associated serrated polyposis

Serrated polyps are considered the precursor lesions of up to 15–30% of all colorectal carcinomas through the serrated pathway, molecularly characterized by the presence of somatic pathogenic variants in *BRAF*, hypermethylation of the promoter regions of tumor suppressor genes and microsatellite instability (Leggett and Whitehall, 2010; Snover, 2011). Serrated polyps are comprised by a heterogeneous group of lesions morphologically characterized by serrated (saw-tooth) architecture of the epithelium that lines the colonic crypts, and which include: hyperplastic polyps, sessile serrated adenomas/polyps, and traditional serrated adenomas/polyps (Rex et al., 2012).

The serrated polyposis syndrome (SPS; MIM# 617108) is a heterogeneous disease defined by the presence of multiple serrated polyps throughout the colon, causing an increased risk (16%) of CRC (Carballal et al., 2016). The clinical definition of SPS is based on the fulfilment of one of the revised World Health Organization (WHO) criteria: i) at least 5 serrated polyps proximal to the sigmoid colon, two of them larger than 10 mm; ii) any number of serrated polyps proximal to the sigmoid colon in an individual with one first-degree relative with SPS; or iii) more than 20 serrated polyps distributed throughout the colon (Snover et al., 2010). Only 10–50% of SPS patients report a family history of CRC (Boparai et al., 2010; Chow et al., 2006; Kalady et al., 2011; Lage et al., 2004; Navarro et al., 2013; Oquinena et al., 2013; Rubio et al., 2006). Being this entity mostly sporadic, -diagnosed between 50 and 60 years of age and believed to be strongly associated with environmental factors (Buchanan et al., 2010; JE et al., 2016; JE et al., 2017)-, it has been suggested that, overall, SPS is not an inherited genetic syndrome but rather behaves as a complex disorder consequence of the interaction of genetic susceptibility and environment. However, evidence indicates that a small proportion of cases may be due to an inherited genetic syndrome.

In 2014, by performing WES in 20 SPS families, Gala et al. identified in two independent families a germline deleterious variant, c.337C > T (p.Arg113*), in the RING-type E3 ubiquitin ligase *RNF43* -inhibitor of the Wnt pathway- (Gala et al., 2014). Moreover, knock out of *RNF43* contributes to an intestinal polyposis phenotype in mice (Koo et al., 2012). Taupin et al. identified the *RNF34* c.394C > T (p.Arg132*) variant in two SPS-affected members of one family (Taupin et al., 2015), and Yan et al., by performing whole-exome sequence analysis of 4 SPS families, identified a deleterious germline variant, c.953-1G > A (p.Glu318fs), in 6 members of one family, 5 fulfilling the revised WHO criteria (Yan et al., 2017). Buchanan et al. assessed the mutation status of *RNF43* in 74 selected SPS families, identifying two rare missense variants, c.443C > G (p.Ala148Gly) and c.640C > G (p.Leu214Val), in two families (Buchanan et al., 2017). Theses variants were predicted deleterious by *in silico* algorithms and later demonstrated to diminish the inhibitory effect of *RNF43* on Wnt signaling (Quintana et al., 2018). No carriers of p.Arg113* or p.Arg132* were detected in 221 additional SPS patients (Buchanan et al., 2017). Recently, Quintana et al. studied *RNF43* mutation status in 96 serrated polyposis patients, identifying one carrier of the p.Arg132* variant in a woman diagnosed with CRC and > 50 polyps (including serrated lesions) (Quintana et al., 2018).

Up to date, a total of 13 carriers (7 families) of *RNF43* (likely) pathogenic variants have been reported, 12 of who are affected with serrated polyposis and/or CRC (mean age at diagnosis: 44; range: 18–65). All colonic lesions analyzed showed *RNF43* somatic loss or mutation (23/23), and 50% (9/18) had the CpG island methylator phenotype (CIMP), a common feature of the serrated pathway. Table 2 depicts the clinical and molecular features of the reported carriers of *RNF43* (likely) pathogenic variants.

The scarce available data suggests that this is an extremely rare syndrome, apparently associated with a high risk to develop serrated polyps and absence of extracolonic manifestations. Nevertheless, data from additional carriers are required to estimate prevalence and penetrance, and accordingly recommend gene-specific surveillance.

2.6. RPS20 mutations as a rare cause of hereditary nonpolyposis CRC

Despite the enormous efforts made for the identification of new genes that could explain the apparently dominantly inherited forms of MMR-proficient nonpolyposis CRC in the last decades, *RPS20*, which encodes a component (S20) of the small ribosomal subunit, is the only candidate gene that has shown consistent association with hereditary nonpolyposis CRC (Valle, 2017). By combining genetic linkage analysis and WES, Nieminen et al. identified a novel truncating *RPS20* variant, c.147dupA (p.Val50Serfs*23), in a Finnish four-generation CRC-affected family. The variant was present in 7 CRC-affected members but neither in 4 cancer-free members nor in one relative diagnosed with breast cancer at age 55. All studied tumors were MMR proficient and did not show loss of the *RPS20* wildtype allele, arguing against the traditional 2-hit mechanism of inactivation of tumor suppressor genes. Patients carrying the *RPS20* c.147dupA variant showed a marked increase of 21S pre-rRNAs, supporting a late pre-rRNA processing defect consistent with haploinsufficiency. No additional *RPS20* (likely) pathogenic variants were identified in 25 Finnish MMR-proficient Amsterdam-positive families and in 61 primary CRCs and cancer cell lines (Nieminen et al., 2014).

Broderick et al. analyzed whole-exome/genome sequencing data from 863 early-onset/familial CRC cases and 1,604 individuals without CRC, and identified a truncating *RPS20* variant, p.Leu61Glufs*11, in a 39 year-old individual with metachronous CRC. They also identified a missense variant, p.Val54Leu, predicted pathogenic, in a 41-year-old CRC patient who fulfilled the Amsterdam criteria for hereditary CRC. No rare missense/disruptive *RPS20* variants were detected in the 1,604 controls (Broderick et al., 2017). So far, only the three CRC families discussed above have been reported to carry *RSP20* (likely) pathogenic variants. Although the scarce available data suggests low prevalence and high penetrance for *RSP20* pathogenic variants, as well as absence of extracolonic manifestations, data from additional carriers are required to estimate risks and recommend gene-specific surveillance measures.

3. Pathogenic variants in other hereditary (non-CRC) cancer genes

CRC is common, specifically in the Western world, and it is therefore not unexpected to find CRC in families with a high burden of cancer. Further, CRC has been observed in families harboring a germline (likely) pathogenic variant in genes not generally associated with CRC. However, there has been conflicting evidence regarding the CRC causality of non-CRC cancer genes. *BRCA1* and *BRCA2,* which are associated with hereditary breast and ovarian cancer (HBOC; MIM# 604370 and 612555), are the most studied genes in this context, and some of the studies are summed up in Table 3. The debate about whether pathogenic *BRCA* variants increase the risk of CRC is still ongoing (Esteban-Jurado et al., 2016; Garre et al., 2015; Kadouri et al., 2007; Kirchhoff et al., 2004; Niell et al., 2004; Phelan et al., 2014; van Asperen et al., 2005). As an example, Garre et al. published evidence of an association between a germline *BRCA2* pathogenic variant and CRC risk. They performed mutation screening of *BRCA2* in 48 probands from families with a dominant inheritance pattern of CRC, but without alterations in any of the known CRC susceptibility genes. The frameshift variant c.3847_3848delGT (p.Val1283Lysfs*2) was found to co-segregate with CRC as well as to present loss of *BRCA2* heterozygosity (LOH) in CRC tumor DNA (Garre et al., 2015). Contrary, Phelan et al. concluded that the risk of CRC is only increased in female carriers of *BRCA1* (likely) pathogenic variants below the age of 50 years, but not

Table 2
Clinical and molecular characteristics of the reported carriers of *RNF43* (likely) pathogenic variants. From (Quintana et al., 2018).

Family (Study)	RNF43 variant (NM_017763)	Polyp number (age at diagnosis) and/or cancer (age at diagnosis)	Co-segregation with the disease in the family	Somatic 2nd hit	[a]BRAF/KRAS	[d]CIMP
Fam-1 (Gala et al., 2014)	c.337C > T (p.Arg113*)	> 30 SSA (51)	n.a.	n.a.	n.a./n.a.	n.a.
Fam-2 (Gala et al., 2014)	c.337C > T (p.Arg113*)	7 SSA (partial/total colectomy) (52) CLL. (42)	n.a. (3 siblings with colonic polyps)	n.a.	n.a./n.a.	n.a.
Fam-3 (Taupin et al., 2015)	c.394C > T (p.Arg132*)	Multiple polyps (23) CRC (23)	Yes	n.a.	n.a./WT	n.a
Fam-4 (Yan et al., 2017)	c.394C > T (p.Arg132*)	> 80 SP (27)	Yes	[b]Yes 100%	16 SP: 62.5% BRAF 18.75% KRAS 5 ad.: 0% BRAF 20% KRAS 1 CRC: WT/WT	13 SP: 61.5% CIMP + 3 ad. and 1 CRC: 100% CIMP-
	c.953-1G > A (p.Glu318fs)	> 100 polyps (SSA, HP, ad.) (65)				
	c.953-1G > A (p.Glu318fs)	> 20 polyps (SSA, HP) (64)				
	c.953-1G > A (p.Glu318fs)	1 HP (3 mm, descending colon) (53) Rectal cancer and 1 ad. (49)				
	c.953-1G > A (p.Glu318fs)	2 SSA and 1 ad. (37)				
	c.953-1G > A (p.Glu318fs)	1SSA and 2 HP (35)				
	c.953-1G > A (p.Glu318fs)	Normal colonoscopy (44) No possibility of colonoscopy (age 44 to 60)				
Fam-5 (Buchanan et al., 2017)	c.640C > G (p.Leu214Val)	> 100 SP (18)	n.a.	n.a.	n.a./n.a.	n.a.
Fam-6 (Buchanan et al., 2017)	c.443C > G (p.Ala148Gly)	34 SP (57)	n.a.	n.a.	n.a./n.a.	n.a.
Fam-7 (Quintana et al., 2018)	c.394C > T (p.Arg132*)	CRC (55) > 40 polyps (serrated)	inconclusive	[c]Yes	1 CRC: WT/WT	1 CRC: CIMP +

Abbreviations: ad., adenoma; CIMP, CpG island methylator phenotype; CLL, chronic leukocytic leukemia; CRC, colorectal cancer; HP, hyperplastic polyp; n.a., not available information; SP, serrated polyp; SSA, sessile serrated adenoma; WT, wildtype.

[a] BRAF V600E and KRAS codons 12 and 13.

[b] All lesions (16 SP, 5 ad. and 1 rectal cancer) from c.953-1G > A carriers studied had either somatic LOH or mutations in *RNF43*.

[c] Somatic splice-site variant: c.2309-1G > A.

[d] CIMP assessed using the ME042-C1 CIMP MS-MLPA kit (MRC-Holland, Amsterdam, the Netherlands). Methylated gene promoters (> 20% methylation): *IGF2, RUNX3, NEURO, CDKN2A, CRABP1*. Unmethylated gene promoters (< 12% methylation): *MLH1, SOCS1, CACNA1G*. DNAs from the patient's blood and a tumor with somatic *MLH1* promoter methylation were included as controls.

Table 3
Studies assessing the prevalence of *BRCA1* and *BRCA2* (likely) pathogenic variants among CRC patients, or the presence of CRC among *BRCA1* and *BRCA2* mutation carriers.

Gene: N	Study group	Study methods	CRC patients carriers of BRCA1/2 mutation	References
BRCA1: 3 *BRCA2*: 3	586 Ashkenazi Jewish women with CRC	Mutation screening for two *BRCA1* and one *BRCA2* founder variants. CC	6/586 (1.02%)	Kirchhoff et al. (2004)
BRCA1: 11 *BRCA2*: 13	1,002 Ashkenazi Jewish patients with CRC	Mutation screening for two *BRCA1* and one *BRCA2* founder variants. CC	24/1,002 (2.4%)	Niell et al. (2004)
BRCA2: 23 (8 below 65 years)	139 *BRCA2* families. Risk in family members (50% probability of being a carrier; n = 1811)	RR for cancer other than BOC (comparing observed numbers with expected)	23/1,811 (1.27%)	van Asperen et al. (2005)
BRCA1: 6 *BRCA2*: 2	1,098 Ashkenazi Jewish women with BOC; *BRCA1*: 229, *BRCA2*: 100 carriers	Clinical genetic testing for *BRCA1* and *BRCA2*	8/329 (2.4%)	Kadouri et al. (2007)
BRCA1/2: 21 *BRCA1*: 8 below 50 years	7,015 women with a *BRCA* mutation	Followed 5,5 years (average) and looked for new cases of CRC	21/7,015 (0.30%)	Phelan et al. (2014)
BRCA2: 2	48 probands with strong familial CRC aggregation; no mutation in CRC genes	Mutation screening of *BRCA2*	2/48 (4.17%)	Garre et al. (2015)
BRCA1: 6 *BRCA2*: 9	1,260 patients tested for Lynch syndrome	Clinical genetic testing with 25-gene NGS sequencing panel	15/1,260 (1.19%)	Yurgelun et al. (2015a)
BRCA2: 3	74 CRC patients with strong familial CRC aggregation; no mutation in CRC genes	WES	3/74 (4.05%)	Esteban-Jurado et al. (2016)
BRCA1/2: 120	252,223 patients of whom 17,743 met hereditary non-polyposis CRC criteria	Clinical genetic testing with 25-gene NGS panel	120/252,223 (0.48%)	Rosenthal et al. (2017)

Abbreviations: BOC, breast or ovarian cancer; CC, case control study; N: number of individuals with CRC and a pathogenic *BRCA* variant; RR: relative risk; WES, whole-exome sequencing.

Table 4
Studies reporting potential association between CRC and non-CRC hereditary cancer genes.

Gene	Study group	Study methods	CRC patients carriers of the corresponding gene mutation	References
BRCA1, BRCA2	See Table 3	See Table 3	See Table 3	See Table 3
CDKN1B, SMARCA4, BARD1, BRIP1	43 CRC patients from 29 families with strong CRC aggregation	WES	4/43 (9.3%)	Esteban-Jurado et al. (2015)
TP53	457 CRC patients at age 40 years or younger (lack of known hereditary cancer syndrome)	Germline sequencing of TP53	6/457 (1.3%)	Yurgelun et al. (2015b)
BRIP1	Clinical genetic testing of 1,260 patients tested for Lynch syndrome	25-gene NGS panel	2/1,260 (0.16%)	Yurgelun et al. (2015a)
ATM, CHEK2, CDKN2A, PALB2	450 patients diagnosed with CRC younger than 50 years	25-gene NGS panel	5/450 (1.1%)	Pearlman et al. (2017)
TP53, PTEN, CDH1, CHEK2	Clinical genetic testing of 252,223 patients; 17,743 met hereditary non-polyposis CRC criteria	25-gene NGS panel	n.a.	Rosenthal et al. (2017)
PALB2, CDKN2A, TP53 CHEK2	Clinical genetic testing of 1,058 unselected CRC patients	25-gene NGS panel	6/1,058 (0.57%)	Yurgelun et al. (2017)
ATM, PALB2	680 unselected CRC patients and 27,728 ancestry-matched cancer-free adults	NGS gene panel of 40 DNA-repair genes	8/680 (1.2%)	AlDubayan et al. (2018)
BRIP1, CHEK2, TP53, XPC	Clinical genetic testing of 98 patients from Amsterdam I/II and Bethesda families	94-gene NGS panel	4/98 (4.1%)	Martin-Morales et al. (2018)

Abbreviations: CRC, colorectal cancer; FA, Fanconi anemia (autosomal recessive); HDGC, Hereditary diffuse gastric cancer; n.a., not available information; NGS, next generation sequencing; WES, whole-exome sequencing.

in women with *BRCA2* variants or in older women. They followed 7,015 women with *BRCA* pathogenic variants for an average of 5.5 years and found 21 new cases of CRC, whereof 8 were in *BRCA1* mutation carriers below 50 years (Phelan et al., 2014). A recent meta-analysis based on 14 studies (Oh et al., 2018), validated some of the results from Phelan et al., finding a potential 1.22-fold greater risk of CRC in *BRCA* pathogenic variant carriers, and this was largely attributable to a 1.48-fold greater risk in *BRCA1* but not in *BRCA2* carriers, regardless of age.

Due to variable design and conflicting evidence of causality in studies investigating the CRC risk in *BRCA* mutation carriers (Table 3) (Sopik et al., 2015), there is still no consensus of whether to screen for CRC in HBOC families. Another aspect to be discussed is whether CRC patients with a pathogenic *BRCA* variant may benefit from treatments used in HBOC (Soyano et al., 2018).

Due to next generation sequencing (NGS) and the increasing use of multigene panel testing and WES, pathogenic variants in other non-CRC hereditary cancer genes have been described recently in familial CRC, pointing to their association with CRC susceptibility (Table 4). Most of these genes have not yet been studied to the same extent as the *BRCA* genes. However, in some cases, such as for carriers of *PTEN* pathogenic variants, CRC screening has been recommended already in the clinical guidelines (Syngal et al., 2015). *PTEN* is associated with Cowden Syndrome, which is a hamartomatous disorder with an increased risk for the development of breast, thyroid and endometrial carcinomas (MIM# 158350). During the last years, hyperplastic, adenomatous and other types of polyps have been described in the colon epithelium of carrier of *PTEN* pathogenic variants, indicating an increased risk for CRC (Stanich et al., 2014). The tumor suppressor genes *TP53* and *CHEK2* may also predispose to CRC (Pearlman et al., 2017; Rosenthal et al., 2017; Yurgelun et al., 2017; Yurgelun et al., 2015a,b). *TP53* germline mutations are associated with Li-Fraumeni syndrome (LFS; MIM# 151623), which predisposes to a wide range of cancers that originally did not include CRC. A *TP53* splice site variant c.783-1G > A, was detected in an atypical family fulfilling both the Chompret criteria for LFS and the Amsterdam II criteria for hereditary non-polyposis CRC (Martin-Morales et al., 2018). Several *TP53* pathogenic variants have been detected in familial or early-onset CRC cases (Rosenthal et al., 2017; Yurgelun et al., 2017; Yurgelun et al., 2015a,b), suggesting an increased CRC risk in LFS families. For this reason, CRC screening is now recommended in LFS families (Kratz et al., 2017). *CHEK2* missense variants c.470T > C (p.Ile157Thr) and c.349A > G (p.Arg117Gly), which are involved in breast and pancreatic cancer predisposition, have also been reported to be associated with CRC (Kilpivaara et al., 2006; Martin-Morales et al., 2018).

Variants in other HBOC genes have been detected in familial CRC. Pathogenic variants in the Fanconi Anemia gene *BRIP1*, associated with a higher risk of ovarian cancer (Rafnar et al., 2011), have been reported recently in familial CRC (Esteban-Jurado et al., 2015; Martin-Morales et al., 2018; Yurgelun et al., 2015a). Mutated *BRCA1*-associated gene *BARD1*, has been also found in a CRC family (Esteban-Jurado et al., 2015). Moreover, *ATM* and *PALB2* have been connected to CRC risk (AlDubayan et al., 2018; Pearlman et al., 2017; Yurgelun et al., 2017). AlDubayan et al. showed significant enrichment of germline pathogenic variants in *ATM* and *PALB2* in CRC individuals compared to cancer-free individuals. In this study, five out of 680 unselected CRC individuals had pathogenic variants in *ATM* whereas three individuals had germline pathogenic variants in *PALB2*. The five individuals with variants in *ATM* had evidence of somatic inactivation of the wild-type allele (LOH or truncating variant) in tumor samples whereas no somatic inactivation was detected in any of the tumors in individuals with germline *PALB2* pathogenic variants (by WES). Seemingly, the basis for tumor initiation and/or progression could be different between these two genes even though they both belong to the HR (homologous recombination) pathway (AlDubayan et al., 2018).

Another non-CRC cancer gene that has been reported in a CRC context is *CDNK2A* (Lynch et al., 2002; Pearlman et al., 2017; Yurgelun

et al., 2017). Pathogenic variants in *CDKN2A* are associated with familial atypical mole melanoma syndrome (FAMMM; MIM# 606719) and are known to predispose to melanoma and pancreatic cancer. Lynch et al. (2002) studied eight FAMMM families with *CDKN2A* germline pathogenic variants. Although there were four cases of CRC in three of these families, there was no information on whether the individuals affected with CRC were carriers of *CDK2A* pathogenic variants (two splice-site and one missense variant). Two of these CRCs were of late onset (age of onset not given for the other two) and may therefore represent sporadic cases (Lynch et al., 2002). Pearlman et al. identified one out of 450 CRC patients younger than 50 years with a *CDKN2A* pathogenic variant, and Yurgelun et al. detected the same *CDKN2A* pathogenic variant (c.9_32dup) in one out of 1,058 unselected CRC patients (Pearlman et al., 2017; Yurgelun et al., 2017). Other genes implicated in rare syndromes that predispose to various kinds of cancer (such as thyroid, renal and pancreatic) have also been detected in hereditary CRC, including *CDKN1B, SMARCA4* (Esteban-Jurado et al., 2015) and *XPC* (Martin-Morales et al., 2018).

In summary, recent studies increasingly report the implication of non-CRC cancer predisposing genes in hereditary CRC. However, the evidence for an increased risk of CRC is not established for most of these genes and must be further studied, to conclude if CRC surveillance should be included in the management of mutation carriers. Although the contribution of pathogenic variants in non-CRC cancer genes to the heredity of CRC is limited compared to the classical CRC genes, it is still relevant. The above studies show a substantial phenotypic overlap among different hereditary cancer syndromes. This observation has raised some concerns suggesting that phenotype-directed genetic testing may sometimes be incomplete. However, the current testing strategy for inherited cancers is moving from single genes towards multigene panel testing, covering the most common hereditary cancer genes.

4. Identification of causal genes

Familial clustering of cancer is caused by genetic and shared environmental factors. However, when environmental factors were assessed between spouses, i.e., when environmental sharing starts in adulthood, even long-term co-habitation appeared to influence only a few cancers, lung, upper aerodigestive tract and skin cancers, and the relative risks were far below the ones known for familial risk at these sites (Schmit et al., 2018; Weires et al., 2011). For colon cancer the relative risk was 1.01 and for rectal cancer it was 0.91 (neither statistically significant), probably surprisingly, in view of the collective belief that diet is important in CRC. The spouse data suggest that genetic sharing (i.e., heritability) is the most important contributor to familial clustering (Frank et al., 2014; Frank et al., 2015). However, identified genes and low-risk loci explain only a small proportion of heritability in cancer (Sampson et al., 2015; Sud et al., 2017; Valle, 2017). For CRC, known high-risk and low-risk genes are thought to account approximately equally, and jointly account for a quarter of familial clustering (Sampson et al., 2015; Sud et al., 2017). In familial CRC the inherited genes are enriched, and the estimates for high-risk genes vary between 17% and 28% depending on the definition of pathogenicity of the variants (Chubb et al., 2016).

4.1. Cancer germline architecture

Until the millennium shift, linkage analysis was the main tool of gene discovery (Rahman, 2014). Of the more than 100 known cancer predisposing genes most were detected using the linkage approach in Mendelian types of families. Most of the 10 high-risk genes predisposing to CRC were also found using such approaches (Turnbull et al., 2018). With the success of this approach fading, many scientists propagated instead for an association study approach based on a paradigm that common diseases, such as cancer, would be caused by common

variants, the 'common disease-common variant' hypothesis. The familial risk conveyed by such variants would be small, which would imply non-Mendelian genetics. By today, such genome-wide association studies (GWASs) have delivered some 600 genomic loci at genome-wide significance, and considering CRC alone, 50 loci have been validated, accounting for ~12% of familial risk of CRC (Nieminen et al., 2014; Schmit et al., 2018). As the risks are low, the clinical utility of the developed 'polygenic risk scores' are debated. Moreover, the newly reported risks of single variants have become very small and views are being expressed that the GWAS era is approaching its end. The GWAS era demonstrated that familial cancers may share a monogenic/oligogenic and a polygenic background which is dependent on cancer type; for CRC the monogenic and polygenic architectures appear equally common, in contrast to some rare cancers and even ovarian cancer, dominated by the monogenic background, and prostate and lung cancer, dominated by the polygenic background.

By now, whole-exome and whole-genome sequencing approaches have revolutionized oncogenomics and have made it an integral part of precision cancer care. However, the main success has been in somatic genetics (tumors) while successes in germline genetics have been limited, including CRC and most other cancers. The successful reports on gene identification for CRC include *POLE, POLD1, NTLH1, MSH3, MLH3* and *RPS20* pathogenic variants in familial CRC and polyposis (Adam et al., 2016; Nieminen et al., 2014; Olkinuora et al., 2018; Palles et al., 2013; Weren et al., 2015a). One reason for success of these studies was the inclusion of families, whereas even large studies on individual familial cases did not produce novel predisposing genes, but have yielded important population estimates on variant frequencies (Chubb et al., 2016).

Information on germline genetic architecture is a relevant guidance to gene identification studies and the methods to be applied. High-risk genes (i.e., relative risk of the order of 10 or more) would cause Mendelian type of clustering with many affected family members over generations. In the Swedish population of 10 million individuals, 29,000 CRCs were diagnosed in one generation, and 3,800 (13.2%) patients had a family history of CRC in parents or siblings; among these only 220 (0.8% of all CRC, 6% of familial CRC) had two or more affected family members which would be suggestive of high-penetrance clustering (Frank et al., 2015). This can be put to a perspective as a recent study reported that 369 Lynch syndrome families were identified in Sweden (Lagerstedt-Robinson et al., 2016). However, these figures are not fully comparable because it is likely that many Lynch syndrome families were identified in an older generation not covered by the above Swedish population data, resulting in 220 high risk families. Yet, the numbers help to delineate the scope of finding novel high-risk CRC genes, which may be limited to extremely rare, perhaps even private pathogenic variants, as has been discussed by others (Turnbull et al., 2018).

4.2. Family based approach and tools

The best approach in search of high-risk genes is to use families. Horn et al., by using the linkage approach, identified a *TERT* promoter mutation in a single large melanoma family. Although promoter mutations in *TERT* are now well known as common somatic drivers in many cancers, only a total of three melanoma families world-wide are known carrying the germline mutation. A contributing factor for selecting this family, in addition to the large numbers of cases amenable to linkage analysis, was that the phenotype was rather unique with early onset and aggressive course (Horn et al., 2013).

The availability of cancer pedigree samples, including also apparently healthy family members is an advantage and needs to be appropriately analyzed. A familial cancer variant prioritization pipeline (FCVPP) has been developed for detection of deleterious germline variants with potential clinical importance in cancer predisposition (Forsti et al., 2016; Kumar et al., 2018). As the first step, a segregation

function for families is included: the variants should be present in cases and not in controls; this step may exclude more than 90% of the potential variants. Likely functionality of the variant is defined by several *in silico* tools, summarized as the CADD score and the variant has to be rare in the European population which is tested by databases such as GnomAD (Genome Aggregation Database; http://gnomad. broadinstitute.org/). The pipeline then uses 12 tools for evaluation of deleteriousness of missense variants and 5 tools for evaluation intolerance of the corresponding genes against functional variants. In assessing non-coding regions the pipeline combines Miranda and Targetscan for 3′ UTR variants and SNPnexus and ChromHMM for detection of transcription binding sites and chromatin modification patterns for 5′UTR variants. The pipeline combines FANTOM5 data and SNPnexus for finding regulatory features of variants located in the enhancer and promoter regions. Genomic Evolutionary Rate Profiling and PhastCons are used for the assessments of conservation across species at the variant position. Ultra-sensitive and sensitive regions are assessed by Funseq2 and ultra-conserved non-coding elements by UCNEbase. At the end of the pipeline usually less than 10 candidate variants survive. These are further assessed through cancer predisposition gene databases, pathway analysis and literature search. The surviving candidates need to be verified by Sanger sequencing and functionality need to be demonstrated using appropriate in vitro tests.

In conclusion, whether the present pipeline leads to discovery of novel cancer predisposition genes does not depend on the pipeline but what is fed in, i.e., pedigree data. Maybe the assumption of a single causal gene may not be correct for the family under study. The numbers of true Mendelian cases increase the power of detection and it is as critical as the correctness of diagnoses. A false assignment of a phenocopy as a Mendelian case or mixing of individuals or samples may have devastating consequences for the analysis. Last but not least, the quality of sequence data and sufficient coverage are important.

5. Candidate genes for hereditary non-polyposis CRC and polyposis

Genomic characterization of the germline DNA of patients with familial CRC has been performed in the last 30 years. Diverse methodologies have been used ranging from classical linkage analysis in large families to the more recent NGS approaches in several small families. Remarkably, this later methodology has boosted the number of candidate genes for hereditary predisposition to this neoplasm. Table 5 summarizes all previous studies proposing new candidate genes for CRC, detected in non-affiliated familial and/or early onset cases for this disease.

Sanger sequencing has been widely used in candidate gene approaches for the identification of germline pathogenic variants in CRC (Coissieux et al., 2011; Guda et al., 2009; Lammi et al., 2004; Richards et al., 1999; Sweet et al., 2005; Zogopoulos et al., 2008), however, most findings have not been replicated in additional cohorts, so far. There is nevertheless evidence in favor of the implication of the *AXIN2* and *ENG* genes in adenomatous and hamartomatous or hyperplasic mixed polyposis, respectively (Lammi et al., 2004; Marvin et al., 2011; Ngeow et al., 2013; Rivera et al., 2014; Sweet et al., 2005).

GALTN12 has been proposed in several studies as a strong candidate CRC susceptibility gene, given linkage and association studies, and inactivating somatic and germline alleles in CRC patients (Clarke et al., 2012; Gray-McGuire et al., 2010; Guda et al., 2009; Kemp et al., 2006; Skoglund et al., 2006; Wiesner et al., 2003). However, *GALTN12* does not seem to be a major high-penetrance gene for CRC predisposition (Lorca et al., 2017; Segui et al., 2014). Recently, Evans et al. defined *GALTN12* as a moderate penetrance gene for CRC (Evans et al., 2018).

With the advent of NGS technologies, numerous studies have emerged to identify new genes of susceptibility to CRC by WES. Initially, these studies did not validate their findings in additional independent cohorts and only proposed candidate genes with more or less

Table 5
Studies performed in non-affiliated familial and/or early-onsetCRC and polyposis and their proposed candidate genes for germline predisposition to this neoplasm.

Study	Approach	Initial cohort	Replication	Functional validation	Candidate gene/s
Richards et al. (1999)	SSCP analysis and sequencing	8 familial gastric cancer cases (1 also CRC)	No	No	CDH1
Lammi et al. (2004)	Linkage analysis and direct sequencing	1 family with oligodontia and CRC	No	No	AXIN2
Marvin et al. (2011)	Direct sequencing	1 family with oligodontia, colonic polyposis, gastric polyps, a mild ectodermal dysplasia and CRC	No	No	
Rivera et al. (2014)	Direct sequencing	23 cases with familial adenomatous polyposis (FAP)	No	No	
Sweet et al. (2005)	DDGE and sequencing	49 patients with hamartomatous polyposis or with hyperplastic/mixed polyposis	No	No	ENG
Ngeow et al. (2013)	DDGE, sequencing and MLPA	603 patients, 119 with personal history of CRC and 461 with < 30 polyps	No	No	
Zogopoulos et al. (2008)	Direct sequencing	116 familial CRC cases	182–1,160 CRC cases and 199–1,133 controls	Yes	EPHB2
Guda et al. (2009)	Direct sequencing	272 CRC patients and 192 controls	No	Yes	GALNT12
Clarke et al. (2012)	Direct sequencing	118 familial CRC cases	No	No	
Segui et al. (2014)	Direct sequencing	103 familial CRC cases	No	No	
Evans et al. (2018)	Direct sequencing	479 CRC cases and 400 controls	No	Yes	
Coissieux et al. (2011)	Direct sequencing	1,801 CRC cases and 4152 controls	No	Yes	UNC5C
Mur et al. (2016)	Direct sequencing	544 familial CRC or polyposis patients (529 families)	No	No	
Smith et al. (2013a)	WES	50 sporadic CRC cases	No	No	FANCM, LAMB4, PTCHD3, LAMC3, TREX2, NOTCH3
DeRycke et al. (2013)	WES	40 familial CRC cases from 16 families	No	No	CENPE, KIF23
de Voer et al. (2013)	Copy number profiling, WES and direct sequencing	72 early-onset CRC cases	146 familial or early-onset CRC cases	Yes	BUB1/BUB3
Mur et al. (2018a)	Targeted sequencing	456 familial CRC cases and 88 polyposis cases	No	Yes	UACA, SFXN4, TWSG1, PSPH, NUDT7, ZNF490, PRSS37, CCDC18, PRADC1, MRPL3, AKR1C4
Gylfe et al. (2013)	WES	96 familial CRC cases	No	No	SEMA4A
Schulz et al. (2004)	Linkage analysis, WES and direct sequencing	1 family with familial CRC type X	53 familial CRC type X cases	Yes	
Tanskanen et al. (2015)	WES	22 early-onset CRC cases	95 familial CRC patients	No	ADAMTS4, CYTL1, SYNE1, MCTP2, ARHGAP12, ATM, DONSON, ROS1, MCTP2
Esteban-Jurado et al. (2015)	WES	43 familial CRC cases from 29 families	No	No	CDKN1B, XRCC4, EPHX1, NFKBIZ, SMARCA4, BARD1
Zhang et al. (2015)	WES	23 CRC cases from 21 early-onset families	No	No	BUB1,LRP5, RPS6KB2, RYR2, EIF2AK4
Weren et al. (2015b)	WES	41 early-onset or familial CRC patients	1,232 early-onset and/or familial CRC patients	Yes	FOCAD
Segui et al. (2015)	WES, targeted sequencing and mutation screening	3 cases from an Amsterdam I MMR-proficient, CRC family	176 MMR-proficient Amsterdam families	Yes	FAN1
de Voer et al. (2015)	WES and targeted sequencing	55 early-onset CRC cases	185 CRC cases and 532 controls	No	BLM
Ngeow et al. (2015)	WES and mutation screening	1 case of familial JPS and gastrointestinal ganglioneuromas	40 JPS cases and 40 CS patients with hamartomatous polyps	Yes	SMAD9
Arora et al. (2015)	WES	20 early-onset CRC cases and 5 early-onset multiple polyposis cases	No	Yes	WRN, ERCC6
Goldberg et al. (2015)	WES and mutation screening	1 family with early-onset CRC, multiple polyps and amenorrhea	170 CRC or polyposis cases	No	MCM9
Thutkawkorapin et al. (2016)	WES	1 CRC and gastric cancer family	98 familial CRC samples and 190 cases from CRC and gastric cancer families	No	DZIP1L, IGSF10, NOTCH1, SF3A1, GAL3ST1
de Voer et al. (2016)	WES and targeted sequencing	55 early-onset CRC cases	174 CRC cases	Yes	PTPN12, LRP6
Hahn et al. (2016)	Targeted sequencing	192 early-onset CRC cases	No	Yes	BUB1B
Spier et al. (2016)	WES and targeted sequencing	12 patients with sporadic adenomatous polyposis	191 polyposis patients	No	DSC2, PIEZO1, ZSWIM7
Adam et al. (2016)	WES	102 colorectal adenomatous polyposis patients	No	Yes	MSH3

Table 5 (*continued*)

Study	Approach	Initial cohort	Replication	Functional validation	Candidate gene/s
Chubb et al. (2016)	WES	1,006 early-onset CRC cases and 1609 controls	5,552 CRC cases and 6792 controls	No	POT1, POLE2, MRE11
Esteban-Jurado et al. (2016)	WES	74 familial CRC cases from 40 families	No	No	BRCA2, BRIP1, FANCC, FANCE, REV3L/POLZ
Brea-Fernandez et al. (2017)	WES and CNV analysis	27 early-onset CRC patients	No	No	AK3, SLIT2
Schubert et al. (2017)	Homozygosity mapping, linkage analysis, exome and whole-genome sequencing	302 CRC cases and 3367 controls	10,554 CRC cases and 21,480 controls	No	MIA3
Hansen et al. (2017)	Targeted sequencing	274 familial CRC cases	No	No	AXIN1, BMP4, CCDC18, NUDT7, PICALM, PTPRJ, SLC5A9, TLR2, TWSG1, UBAP2, USP6NL, ZFP14
Martin-Morales et al. (2017)	WES	1 family with familial CRC type X	No	Yes	SETD6
Bellido et al. (2018)	WES and targeted sequencing	1 familial CRC family	547 familial or early-onset CRC cases	Yes	BRF1
Yu et al. (2018)	WES and SNV genotyping	1 family with familial CRC type X	81 CRC cases and 12 controls	No	DDX20, ZFYVE26, PIK3R3, SLC26A8, ZEB2, TP53INP1, SLC11A1, LRBA, CEBPZ, ETAA1, SEMA3G, IFRD2, FAT1
Franch-Exposito et al. (2018)	WES and CNV analysis	74 familial CRC cases from 40 families	No	No	TTF2, TMEM158

Abbreviations: CNV, copy number variant; CRC, colorectal cancer; DDGE, denaturation gradient gel electrophoresis; JPS, juvenile polyposis syndrome; MLPA, multiple ligation probe amplification; MMR, mismatch repair; SNV, single nucleotide variant; SSCP, single-strand conformation polymorphism; WES, whole-exome sequencing.

evidence of causality for hereditary CRC. They just reported a detailed list of rare (MAF ≤ 1%) and loss-of-function candidate variants in genes that had been selected according to either their role in CRC carcinogenesis, potential implication as tumor suppressors, presence in genetically enriched subsets of early-onset CRC cases, absence in healthy controls, or cosegregation of the variants within the families (Brea-Fernandez et al., 2017; Chubb et al., 2016; de Voer et al., 2016; DeRycke et al., 2013; Esteban-Jurado et al., 2015, 2016; Gylfe et al., 2013; Smith et al., 2013a; Spier et al., 2016; Tanskanen et al., 2015; Thutkawkorapin et al., 2016; Yu et al., 2018).

The development of genome-wide copy number arrays and massive parallel sequencing resulted in a shift of techniques used in the quest for finding novel genes predisposing to CRC and polyposis. Where previously genome-wide linkage analysis and candidate gene approaches were used, nowadays genome-wide copy number analyses (CNA), WES and more recently whole-genome sequencing (WGS) are employed to identify novel genes predisposing to CRC and polyposis. As these genome-wide techniques are less time-consuming and less or equally expensive, isolated cases and cases with a less clear familial history for CRC are included in discovery and replication cohorts. These approaches have resulted in the identification of several novel high-penetrant CRC and polyposis predisposing genes, such as POLE, POLD1 and NTHL1, but have also resulted in a compilation of candidate genes, for which much more evidence is required before they can be implemented in daily clinical genetics practice.

Variants in several components involved in the spindle assembly checkpoint, which ensures proper chromosome segregation during mitosis, are associated with CRC predisposition, such as BUB1B, BUB1 and BUB3 (de Voer et al., 2013; Mur et al., 2018a; Rio Frio et al., 2010). BUB1B was identified in a single isolated case and has remained the only case thus far, probably as a result from a unique homozygous variant resulting in very low levels of BUBR1 (Hahn et al., 2016; Rio Frio et al., 2010). Evidence from functional studies on BUB1 and BUB3 variants suggest pathogenicity for several variants (de Voer et al., 2013; Mur et al., 2018a), while other studies do not find any association (Broderick et al., 2017).

For several other candidate CRC and polyposis predisposing genes indirect functional evidence on pathogenicity has been gathered, such as WRN, ERCC6, SEMA4A, SMAD9, SEMA4A, FAN1, FOCAD, LRP6, MSH3, SETD6 and BRF1 (Adam et al., 2016; Arora et al., 2015; Bellido et al., 2018; de Voer et al., 2016; Martin-Morales et al., 2017; Ngeow et al., 2015; Schulz et al., 2004; Segui et al., 2015; Weren et al., 2015b). Several of these genes, such as WRN, ERCC6 and FAN1, play a role in the DNA damage response, whereas others play a role in focal adhesion (FOCAD), semaphorin signaling (SEMA4A), TGF-β signaling (SMAD9), WNT signaling (LRP6 and SETD6), DNA MMR (MSH3), and transcription initiation (BRF1).

Besides WES, other approaches have shed additional light into this area. Targeted sequencing of previously selected genes has also been applied to some extent yielding additional candidate genes (Hahn et al., 2016; Hansen et al., 2017). A combination of homozygosity mapping, linkage analysis and exome and whole-genome sequencing proposed MIA3 as an additional candidate gene (Schubert et al., 2017). CNV approaches to identify mutational events with a putative involvement in CRC germline predisposition have also been explored (Brea-Fernandez et al., 2017; Franch-Exposito et al., 2018).

In summary, it remains to be elucidated if the majority of these candidate genes will play a role in predisposition to CRC and/or polyposis, which will likely be facilitated in the next decade once WES or WGS is implemented in routine genetic diagnostics.

6. Conclusions

As other complex diseases, CRC is caused by both genetic and environmental factors. Twin studies showed that around 13%–30% of the variation in CRC susceptibility involves inherited genetic differences. In

that sense, a minority of CRC cases (∼5%) show strong familial aggregation and belong to the well-known hereditary CRC forms, mainly caused by germline pathogenic variants in known high-penetrance hereditary genes such as *APC*, *MUTYH* and the DNA MMR genes. Recently, NGS studies have identified new high-penetrance CRC hereditary genes, and a large number of candidate genes that require further evidence to be implemented in routine genetic testing. This review described recent advances and new genes lately described to be involved in hereditary CRC. For the newcomers in this scenario, it remains to be elucidated if the majority of these candidate genes will play a relevant role in predisposition to CRC and/or polyposis, which will be likely facilitated in the next decade once WES or WGS are implemented in routine genetic diagnostics.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mam.2019.03.001.

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