Translational Research in Familial Colorectal Cancer Syndromes

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Abstract

Keywords

- familial colorectal cancer
- Lynch syndrome
- FAP
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- POLE/POLD1

Growing knowledge of inherited colorectal cancer syndromes has led to better surveillance and better care of this subset of patients. The most well-known entities, including Lynch syndrome and familial adenomatous polyposis, are continually being studied and with the advent of more sophisticated genetic testing, additional genetic discoveries have been made in the field of inherited cancer. This article will summarize many of the updates to both the familiar and perhaps less familiar syndromes that can lead to inherited or early-onset colorectal cancer.

In the past two decades, our understanding of inherited colorectal cancer (CRC) syndromes has increased greatly. From advances in molecular and genetic testing to recognition of new syndromes, the field of familial CRC is ever expanding both in the laboratory and in the clinical realm. Along with updates on the management and testing of Lynch syndrome (LS) and familial adenomatous polyposis (FAP), we now have to consider mutations such as POLD1/POLE and newer clinical entities including serrated polyposis syndrome (SPS). There is also growing evidence that CRC is increasing in those younger than 50 years, which is a population that has a higher likelihood of a potentially inherited component.

Additionally, knowledge and use of the mutations in hereditary syndromes including FAP and LS has benefitted the study of colon cancer, specifically in a mouse model. The incidence of spontaneous CRC in rodents is less than 1%, which can be increased to 30 to 40% in in-bred WF-Osaka rats, but the behavior of disease is different from human cancer with no progression to metastatic spread and often signs of spontaneous regression. In contrast, the genetically engineered mouse models, using engineered adenomatous polyposis coli (APC) or mismatch repair (MMR) defects, have revealed phenotypes that are similar to human colon cancer and polyposis allowing for greater study of anticancer candidate therapies.¹

This article highlights many of the updates and newer data in a growing body of literature on hereditary CRC.

Genetic Testing

Mutations in at least 10 genes are recognized to cause Mendelian syndromes associated with CRC for which genetic testing can be offered. The advent of next-generation sequencing (NGS) allows for comprehensive mutational screening of CRC susceptibility genes. The cost of exome analysis is likely to drop in the near future with increasing capacity and automation. Currently, for regions of high sequence coverage, concordance between exome sequencing and conventional Sanger sequencing is high, but is set to improve as NGS technology becomes even more robust.²

There are many companies that specialize in genetic testing. Ambry Genetics utilizes a targeted NGS platform for all of their cancer panels, but also uses Sanger sequencing to confirm all mutations, variants likely pathogenic (VLPs), and variants of uncertain significance (VUSs) that are found through NGS (personal communication: Kelly Fulk, MS, CGC, Oncology Genetic Specialist, Ambry Genetics, March 15, 2016). In a similar fashion, Myriad uses a NGS platform, but all clinically significant variants that are identified and regions that do not meet NGS quality metrics are independently confirmed with site-specific Sanger sequencing.³ Not all seemingly inherited CRC has an associated gene mutation; however, there are multiple that do. ➤ **Table 1** outlines the known associated genetic mutations and their syndromes. There are clearly CRC patients with a strong family history of

Table 1 Known mutations associated with early-onset colorectal cancer syndromes that can be tested by NGS^{6,26}

Associated gene	Syndrome	Consider testing	Associated tumors	Inheritance
Mismatch repair genes (<i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i> , <i>EPCAM</i>)	Lynch syndrome	If patient meets Amsterdam II; if tumor meets Bethesda criteria; if tumor has MSI-H or absence of IHC	Endometrial; urinary tract, stomach	Autosomal dominant
<i>APC</i>	Familial adenomatous polyposis	If patient has ≥ 20 adenomatous polyps	Small bowel, stomach, thyroid, liver (hepatoblastoma), desmoid	Autosomal dominant
<i>MutYH</i>	MYH-associated polyposis	If patient has ≥ 20 but < 100 polyps	Small bowel, stomach	Autosomal recessive
<i>STK11</i>	Peutz Jeghers syndrome	Perioral or buccal pigmentation and/or ≥ 2 histologically characteristic GI hamartomatous polyps or a family history of Peutz Jeghers syndrome	Stomach, small bowel, pancreas, breast, ovarian, uterus, cervical, testicular, lung	Autosomal dominant
<i>Smad4/BPMR1A</i>	Juvenile polyposis syndrome	At least 5 juvenile polyps in the colorectum; juvenile polyps in other parts of the GI tract; or any number of juvenile polyps in a person with a family history of juvenile polyps	Upper GI cancer (stomach, pancreas, and small bowel)	Autosomal dominant
<i>POLD1/POLE</i>	Polymerase proofreading-associated polyposis	See ► Table 2	Endometrial, duodenal adenomas	Autosomal dominant

Abbreviations: GI, gastrointestinal; IHC, immunohistochemistry; MSI-H, microsatellite instability–high; NGS, next-generation sequencing.

CRC whose genetic testing does not reveal any mutations in known genes, but they must harbor a yet to be determined mutation. These patients should be treated and aggressively surveilled based on their personal and family history of CRC, regardless of their lack of a known mutation.

Specific Syndromes

Mismatch Repair Deficiency-Related Syndromes

LS, perhaps the most well-known as it is the most common inherited CRC syndrome, affects up to 3% of all CRC patients. The genetic basis of LS was determined in part through basic science research on DNA repair in yeast and bacteria.⁴ It results from a germline mutation in one of the DNA MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) or from the loss of expression of *MSH2* by the deletion of *EPCAM*.⁵ The other copy of the affected gene in these patients is then sporadically mutated resulting in failure of MMR and rapid progression of a colon polyp to a cancer. The adoption of microsatellite instability (MSI) and immunohistochemistry (IHC) testing on tumors has increased our ability to detect LS and thus counsel our patients about treatment and surveil-

lance options. Two evolving areas of LS-related research include the treatment of MSI-high (MSI-H) cancers with 5-FU-based chemotherapy as well as chemoprevention in patients with LS.

Chemotherapy in MSI-H CRC

Among the 12 to 15% of all CRCs with MSI-H tumors, one-third of CRCs are LS and two-thirds are sporadic. The sporadic MSI-H tumors develop in a background of dense promoter hypermethylation of cancer-specific genes known as the CpG island methylator phenotype (CIMP). Approximately half of the sporadic MSI-H cases are associated with BRAF mutations, which helps distinguish them from LS cases. While the most important factor in determining prognosis of CRC is the tumor stage, there are factors such as MSI that contribute stage-independent variability in outcomes. This appears to be stronger in earlier-stage tumors such as stage II, than it does in stage III tumors. In multiple studies, the presence of MSI in stage II and stage III confers a better overall prognosis; however, the controversy lies in the addition of 5-FU-based chemotherapy to the treatment of these patients. 5-FU-based chemotherapy is the most commonly used therapy

for the treatment of CRC. Chemotherapy is used selectively in stage II based on higher-risk features,⁶ but it has been shown repeatedly that its use in patients with stage II MSI-H cancer has no benefit or may even have worse outcomes.^{7–10} However, in stage III CRC patients, a significant survival benefit from surgery + 5-FU was seen in MSI-H tumors, which supports the use in treatment of stage III disease.¹⁰ It is important to note that many of these studies used 5-FU as monotherapy or in combination with levamisole or leucovorin. When looking at treatment regimens adding oxaliplatin, there are limited available data for the predictive impact on the outcome of MSI-H tumors. There is suggestion, however, that MSI-H tumors are susceptible to oxaliplatin based on a preclinical study by Fink et al.¹¹ In addition, in a retrospective study looking at stage III colon cancers all treated with FOLFOX, the MSI status was still a prognostic factor with improved disease-free survival, suggesting benefit from chemotherapy.¹² Additionally, in the 10-year follow-up to the MOSAIC trial, FOLFOX conferred an improved disease-free survival benefit in both the patients with MSI and microsatellite stability (MSS).¹³ In a small study that notes it is underpowered, Gavin et al looked at whether or not MSI or MMR status can predict response to oxaliplatin efficacy and showed that it was not predictive. Thus, the assumption would be that any benefit induced by oxaliplatin is similar in MSI and MSS tumors.¹⁴ The updated recommendations for MSI tumors in the NCCN guidelines state that MSI testing should be performed for all patients with stage II disease, because stage II MSI-H patients may have a good prognosis and may not benefit from 5-FU adjuvant therapy.⁶ However, the available data and the NCCN guidelines support the use of oxaliplatin-based adjuvant chemotherapy for all stage III disease regardless of MSI status.^{6,15}

These studies do not differentiate LS tumors from sporadic MSI-H tumors and it is not completely clear how similar the development of CRCs is in these populations. As mentioned previously, sporadic MSI tumors are more commonly associated with enhanced CIMP, which may lead to downregulation of subsets of genes not affected in LS. Sporadic MSI-H tumors are also associated with *BRAF* mutations, which is untrue in LS, and may play a role in the response to therapy.⁴ Currently, there are no data to support treating sporadic or inherited MMR mutations differently, but it raises an interesting question.

Chemoprevention in Lynch Syndrome

The observation that the use of nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin was less common among those who developed CRC than in people who did not was made in 1988 by Kune et al.^{16,17} Other observational studies supported this, but in 2012 a randomized controlled trial, the CAPP2 study (Colorectal Adenoma/Carcinoma Prevention Program), was published. This study demonstrated that taking 600 mg of aspirin daily for at least 2 years results in a reduction in CRC of 63% in patients with LS. This effect becomes significant 5 years after initiation of the intervention with an incidence ratio of 0.37 (CI: 0.18–0.78). There was no significant difference in adverse events between the

placebo and aspirin group.¹⁷ CAPP3 trial is still accruing but will look at the effect of various doses of aspirin.

A recently published article evaluated the effect of aspirin and ibuprofen on the risk of developing CRC in patients with LS and found that any regular use for longer than 1 month began to decrease the risk of CRC.¹⁸ The argument for the use of NSAID for prevention is strengthening, but the current consensus statement from the U.S. Multi-Society Task Force on Colorectal Cancer regarding LS is that there is growing but not conclusive evidence that use of aspirin is beneficial in preventing cancer in LS patients. Treatment of an individual patient with aspirin is a consideration after discussion of patient-specific risks, benefits, and uncertainties of treatment is conducted.¹⁹ Regarding surgical recommendations, the same group states that in patients with colon cancer or a colorectal neoplasia not removable by endoscopy and known LS, colectomy with ileorectal anastomosis is recommended. With the caveat that if the patient is older than 60 to 65 years, consideration for less extensive surgery should be made.¹⁹

Other Syndromes with Similarities to Lynch Syndrome

Lynch syndrome was once used synonymously with hereditary nonpolyposis colon cancer (HNPCC); however, now the presence of an identified germline mutation demarcates LS. Thus, there are newly defined syndromes that fall under the umbrella of HNPCC as a clinical definition. These include Lynch-like syndrome and familial colorectal cancer type X (FCCTX).

Lynch-like syndrome is used to describe patients who lack a germline MMR gene mutation but have MSI-H tumors or absence of MMR IHC protein staining. Similar to Lynch, they do generally present with cancer at a younger age, and do have a higher incidence of CRC than the general population (standardized incidence ratio (SIR) SIR 2.12).²⁰ Lynch-like syndrome's lack of mutation could be due to limitations in current genetic testing that may not allow detection of some germline mutations. An alternative theory is that DNA MMR can be inactivated by other mechanisms, which result in similar clinical manifestations as LS.⁵

FCCTX is the new term applied to patients who meet clinical criteria for HNPCC (Amsterdam criteria), but their tumor is microsatellite stable and does not have a germline MMR gene mutation. Similar to Lynch-like syndrome, these patients have an approximately twofold increase in CRC incidence compared with the general population.^{5,21}

Little is known about the causes of Lynch-like syndrome and FCCTX; thus, risk is difficult to predict, but it has been suggested that until we have more information regarding cancer risks and rates of progression, intensive surveillance for CRC, similar to LS, should occur.⁵

Constitutional mismatch repair deficiency syndrome (CMMRD) is a relatively rare disorder that is inherited in an autosomal recessive fashion. CMMRD is caused by inheriting biallelic MMR gene mutations. Early-onset cancer is common. Nearly all CMMRD patients exhibit cutaneous café-au-lait spots²² and other features may mimic neurofibromatosis type 1, including Lisch nodules of the iris and axillary freckling.²³ CMMRD may also be clinically difficult to

distinguish from the adenomatous polyposis syndromes, as multiple intestinal adenomas may develop.²⁴ Up to 40% of patients develop two primary malignancies and at least 50% develop digestive tract cancers, generally in the second and third decades of life.²³ The majority of CMMRD cases are biallelic *PMS2* mutations (60%), although the syndrome can be related to any of the four MMR genes.²⁵ The increased association with *PMS2* mutations may be because the penetrance of a *PMS2* mutation is lower than with *MLH1* or *MSH2* and the parents may not be aware of their mutation because they are not affected.²³ Once identified, the surveillance recommendations per the CMMRD Consortium include a colonoscopy, EGD, and capsule endoscopy annually beginning at the age of 3 or at the initial diagnosis, a brain ultrasound at birth then MRI every 6 months, as well as laboratories every 4 months. Once a patient reaches adulthood, a uterine ultrasound annually and a renal ultrasound with urine cytology each year are recommended.²²

Familial Adenomatous Polyposis

FAP is caused by a germline mutation of the adenomatous polyposis coli (*APC*) gene, which is on chromosome 5q21. *APC* is a tumor suppressor gene and with one mutated inherited gene, adenoma formation is initiated when the second allele is damaged or lost in a stem cell of the colonic crypt. The attenuated form (AFAP) arises from an *APC* mutation at either the far proximal or far distal end of the gene or in exon 9.²⁶ The most recent NCCN guidelines include a recommendation for testing for *APC* and *MUTYH* genetic abnormalities in patients with a personal history of ≥ 20 adenomas, previously it was ≥ 10 .⁶

Chemoprevention is an area of active study for FAP with the goal of slowing down growth of new adenomas and progression of existing adenomas. Cyclooxygenase enzymes (COX-1 and COX-2) have been the target of study for many chemoprevention trials, as specifically COX-2 is increasingly implicated in the adenoma-carcinoma sequence. With the help of genetically engineered mice with an *APC* mutation, inhibition of COX-1 and 2 has been shown to reduce polyp burden in FAP and demonstrate partial suppression of the adenomatous phenotype in those with a COX-2 deficiency.^{1,27} The CAPP1 trial looked at aspirin and resistant starch for prevention and treatment of adenomas in FAP. This randomized study included 133 FAP patients in the primary analysis but did not find significantly reduced polyp count in the rectum and sigmoid colon in any of the treatment groups. There was a trend toward a smaller size of large polyps in the aspirin group, but it was not significant until more than 1 year from the initiation of the intervention.²⁸ A selective COX-2 inhibitor, celecoxib, has also been evaluated in a randomized trial, which showed that after 6 months of 400 mg twice daily, there was a significant reduction in the number of colorectal polyps.²⁹ There is currently a study underway looking at the combination of NSAIDs and difluoromethylornithine (DFMO) as a primary chemopreventative agent in FAP. DFMO inhibits ornithine decarboxylase, which is the first enzyme in the polyamine synthesis and found to

be elevated in patients with FAP.²⁷ Other agents including curcumin in tumeric, vitamin c, and calcium have been studied; however, to date there is no recommendation by the NCCN for use of a chemopreventative agent. There are no FDA-approved medications either for the primary use of chemopreventative agents in FAP or to facilitate management of the remaining rectum after surgery where the rectum or a portion of it is left in place.⁶

Serrated Polyposis Syndrome

Previously known as hyperplastic polyposis, serrated polyposis is a clinical diagnosis made in patients who have met at least one of the following criteria: (1) at least five serrated polyps proximal to the sigmoid colon with two or more being greater than 10 mm; (2) any number of serrated polyps proximal to the sigmoid colon if the individual has a first-degree relative with serrated polyposis; or (3) more than 20 serrated polyps of any size but distributed throughout the colon.⁶ Currently, there is not one causative gene that has been identified as the cause of this syndrome, but there have been case reports of associated genes in severely affected kindred. Taupin et al reported a family with two siblings who met clinical criteria for SPS and had a novel mutation in *RNF43*. *RNF43* encodes a ubiquitin ligase that plays a role in the Wnt signal pathway.³⁰ A mutation in the same gene was found in two other unrelated sporadic SPS patients evaluated by Gala et al.³¹ Continued testing will hopefully lead to more candidate genes to help with the diagnosis and treatment of this syndrome.

The prevalence of SPS in colonoscopy screening populations is 1/2,000, but the rate in the general population is unknown.³² The risk of CRC at first presentation with SPS has been reported as high as 50%; however, in the largest study to date, IJspeert et al showed a lower incidence.³³ They identified 480 patients with SPS in a seven-hospital retrospective cohort with 434 who met inclusion criteria. Overall, 29.3% of patients were diagnosed with CRC, of whom 1.8% had two synchronous primary CRCs. The median age at diagnosis of first CRC was 60.8 years. In the study population, they looked at risk factors for CRC and, in a logistic regression analysis, found that patients having at least one serrated polyp with dysplasia increased the odds ratio (OR) by 2.07 (95% confidence interval [CI]: 1.28–3.33). The presence of at least one advanced adenoma also increased the OR for cancer development to 2.30 (95% CI: 1.47–3.67). Interestingly, patients with a history of smoking had a lower risk of CRC (OR: 0.36, 95% CI: 0.23–0.56). The authors postulated that the effect of smoking may be mainly observed on the diminutive polyps, thus decreasing the overall risk of CRC as fewer polyps exist. This is supported by the fact that significantly more of those patients with a history of smoking fulfilled criteria 3 only when compared with non-smokers (OR: 1.7, 95% CI: 1.1–2.7).³³

Ninety-two percent of patients with SPS were able to be endoscopically cleared of all clinically relevant lesions and were followed with colonoscopy. The median interval between follow-up colonoscopies was 1.2 years with a median

Table 2 Proposed guidelines for genetic testing for PPAP

POLE	POLD1
Attenuated adenomatous polyposis (20–100 adenomas)	Attenuated adenomatous polyposis (20–100 adenomas)
Amsterdam I (only CRC)	Amsterdam II (only CRC and EC)
CRC and oligopolyposis, both diagnosed before age 50	CRC before age 50 or EC before age 60, and oligopolyposis diagnosed before age 50
CRC or oligopolyposis and first-degree relative with CRC diagnosed before age 50	CRC or EC or oligopolyposis and first-degree relative with CRC before age 50 or EC before age 60
CRC or oligopolyposis and two or more first- or second-degree relatives with CRC	CRC or EC or oligopolyposis and two or more first- or second-degree relatives with CRC or EC

Abbreviations: CRC, colorectal cancer; EC, endometrial cancer; oligopolyposis, 5–20 adenomas; PPAP, polymerase proofreading-associated polyposis.

Source: Adapted from Bellido et al.³⁵

follow-up of 3.2 years. They concluded that the 5-year cumulative incidence of CRC during surveillance was 1.5%.³³ This aligns with the NCCN guidelines recommending colonoscopy with polypectomy until all polyps ≥ 5 mm are removed, and then colonoscopy every 1 to 3 years depending on number and size of polyps. The guidelines do state that clearing of all polyps is preferable if possible. If colonoscopic treatment is inadequate or if high-grade dysplasia occurs, a consideration for surgical resection should be made.⁶ Relatives of patients with SPS should undergo a screening colonoscopy when they are an age equal to the youngest age of onset of SPS diagnosis in their relative, age 40, or 10 years earlier than a relative with CRC complicating SPS, whichever of these criteria come first. This should be repeated every 5 years if no polyps are found, but if proximal serrated polyps or multiple adenomas are found, it should be repeated every 1 to 3 years.⁶

Polymerase Proofreading-Associated Polyposis

Described by Palles et al, this syndrome is caused by a germline mutation in the exonuclease domain of *POLE* or *POLD1*. It can present with multiple or large adenomas and early-onset CRC with MSS. They performed whole-genome sequencing to evaluate for potentially pathogenic mutations and found that mutations in *POLE* L424V demonstrated a phenotype consistent with a dominantly inherited, high penetrance predisposition to colorectal adenoma and carcinoma. There was no evidence of associated extracolonic tumors with the *POLE*-mutated families. Additionally, they found *POLD1* S478N mutations that were phenotypically similar to those with the *POLE* mutation. However, several affected individuals with the *POLD1* mutation developed endometrial cancer and one had a brain tumor. *POLE* is thought to cause adenomatous and cancerous changes by decreasing fidelity of replication-associated polymerase proofreading, leading to an increased mutation rate by base substitutions. *POLD1* is also thought to affect proofreading.³⁴ Additional mutations have been detected in *POLD1* that appear to be pathologic. Bellido et al identified 69 carriers of *POLE/POLD1* mutations and found that in the

POLD1 mutation carriers, CRC was diagnosed in 64% with 57% of the female carriers having endometrial tumors and 14% of the female carriers having breast tumors. The mean age at diagnosis for *POLE*-associated CRC was 40.7 years and for *POLD1* was 35.9 years.³⁵ Their recommended testing for *POLE/POLD1* mutations is illustrated in ►Table 2.

Colorectal Cancer in Patients Younger Than 50 years

Current screening guidelines recommend starting colonoscopy in average-risk patients at the age of 50 years. This has recently come under scrutiny, as more data are supporting the increase in incidence of CRC in the younger population. Younger-onset CRC is thought to have a stronger hereditary component, although in most cases assessed, no known genetic mutation is identified. Goldvaser et al looked at their institution's CRC population and stratified them by age ≤ 40 or age ≥ 50 to attempt to define clinicopathologic differences in the populations. As expected for the younger group, the diagnosis usually follows the development of symptoms. Interestingly, a higher rate of rectal tumors was found in the younger group with an increased risk of the tumor demonstrating characteristics including lymphovascular invasion, grade III (high grade), and signet ring features. They were also diagnosed at a higher stage when younger. When the researchers compared stage-specific disease-free and overall survival at 5 years, this study found no difference.³⁶ Abdelsattar et al found adjusted cancer-specific survival to be better in younger patients across all stage groups.³⁷ Another study looked at the trend of CRC among young adults aged 20 to 49 years using SEER database and found an increase by 1.5% per year in men and 1.6% per year in women from 1992 to 2005. The largest annual percent increase in the groups they evaluated was the youngest age group, 20 to 29 years, by 5.2% per year in men and 5.6% per year in women. They postulated that it may, to some degree, be due to environmental change over time, including higher obesity rates, increased consumption of red and processed meats with decreased milk, and higher calcium consumption.³⁸ Ballester et al cited the histologic features more typically associated with young-onset CRC, including mucinous, signet ring, poor

differentiation, suggesting that the molecular biology of tumors in the young is different. They described the subset of CRCs defined as microsatellite and chromosome stable (MACS) that occur most frequently in younger cases. Some have even suggested that MACS may be related to familial CRC syndromes due to the increased frequency in the young.³⁹ To date, however, there is still significant heterogeneity in the underlying mechanisms of young-onset CRC and further study is needed.

Conclusion

Inherited CRC is a fascinating area of study with continued opportunity for improvement in both the detection and treatment of this subset of patients. With rapid advances in genetic technology, the next decade promises to hold as much or more growth as the last.

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