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ELENCO N. 1

- I microsatelliti e loro utilità nella gestione del cancro colon-rettale.

- Quali software possono essere utilizzati per la gestione della bibliografia scientifica?

Hereditary Colon Cancer Syndromes

Manish Gala and Daniel C. Chung

Colon cancer is associated with a family history in up to 25% of cases. As many as 5% are associated with an established hereditary syndrome, demonstrating the profound influence of inheritable genetic mechanisms in the development of this disease. These syndromes confer a diverse spectrum of risk, age of presentation, endoscopic and histological findings, extracolonic manifestations, and modes of inheritance. As the molecular characteristics of these disorders become better described, enhanced genotype-phenotype correlations may offer a more targeted approach to diagnosis, screening, and surveillance. While the strategies for diagnosis and management of familial adenomatous polyposis (FAP) and Lynch syndrome are more established, the approach to newly recognized syndromes such as *MUTYH*-associated polyposis (MAP) and hyperplastic polyposis syndromes continues to evolve. Effective cancer prevention in affected individuals and at-risk family members first requires timely recognition of these hereditary colon cancer syndromes followed by integration of genetic testing and clinical examinations.
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Colorectal cancer remains the third most common cancer diagnosed among men and women in the United States, with 142,570 new cases projected to occur in 2010.[1] Despite a reduction in the age-adjusted incidence rate from 54.4 to 45.5 per 100,000 persons between 2000 and 2007, an estimated 51,370 deaths are expected to occur in 2010, accounting for approximately 9% of all cancer deaths.[1,2] In addition to lifestyle modifiers, genetic risk factors are known to play a significant role in the development of colon cancer. While as many as 25% of cases are associated with a family history of the disease, 5% of cases develop in the setting of an established familial genetic syndrome.[3,4] As the catalogue of inheritable genetic mechanisms expands, the ability of healthcare providers to identify such patients and affected family members for appropriate counseling, screening, and surveillance will be critical for effective cancer prevention and management.

Recognition of hereditary colon cancer syndromes first requires the raised suspicion of the thoughtful clinician. In addition to a carefully documented family history, age of presentation, personal and family history of extracolonic tumors, endoscopic findings, and physical examiantion findings can be important clues to establishing a diagnosis. Frequently divided into nonpolyposis or polyposis colon cancer syndromes, we will discuss the salient features and management strategies for these disorders.

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POLYPOSIS SYNDROMES

Familial Adenomatous Polyposis/Attenuated Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is the most common polyposis syndrome, with a prevalence of one in 5,000-7,000 persons.[5] Characterized by the progressive development of hundreds to thousands of adenomatous colonic polyps beginning in the second decade of life, it carries a 100% percent risk of colorectal cancer (see Figure 1). Compared to the median age of diagnosis of 70 years for sporadic cases, colon cancer develops in patients with FAP at 40 years, or 10 to 15 years after the initial development of polyposis.[2] Transmitted in an autosomal dominant fashion, FAP exhibits 100% penetrance among affected individuals.

Attenuated adenomatous polyposis (AFAP) typically presents with an oligopolyposis of less than 100 adenomas with a right-sided predominance and flat morphology.[6] The lifetime risk of colorectal cancer is not as inevitable as with FAP, but it is still estimated to be up to 69%. The median ages of onset of polyposis and colorectal cancer are 35-45 years and 55 years, respectively.[7] This delay in presentation and reduced polyp number compared to classic FAP can make the diagno-

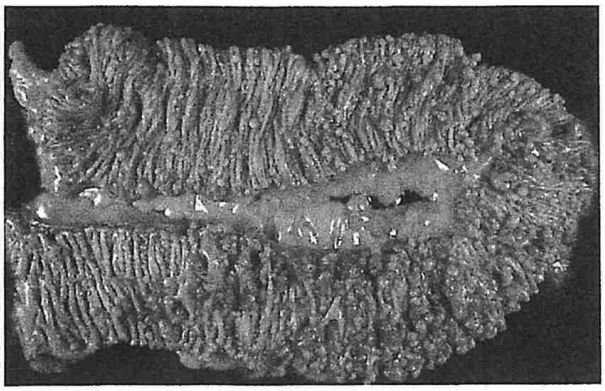

Figure 1. Gross pathology specimen from a FAP patient undergoing total colectomy. The colon is carpeted with hundreds to thousands of adenomatous polyps. (Photo courtesy of Dr Mari Mino-Knudson, Massachusetts General Hospital Department of Pathology.)

sis difficult. Genetic testing may be required to differentiate AFAP from sporadic cancers and other syndromes such as Lynch.[8]

There are several important extracolonic manifestations associated with FAP/AFAP. More than 90% of patients with FAP will develop duodenal, ampullary, or peri-ampullary adenomas, with 5% to 10% of patients developing duodenal carcinoma by age 60.[9,10] Fundic gland polyps and antral adenomas are also quite common and are usually benign. The risk of gastric adenocarcinoma is less than 1% in Western populations.[11] The risks of upper intestinal lesions are similar for AFAP.[8] Other extracolonic cancers include follicular and papillary thyroid cancers, which may precede the development of polyposis and present in up to 12% of patients.[12] Hepatoblastoma has been observed in a subset of young children.[13] Turcot syndrome, the presence of CNS tumors with a hereditary colon cancer syndrome, can present with medulloblastomas, and less commonly with gliomas.[14] Benign growths such as desmoids, osteomas, supernumerary teeth, epidermoid cysts, congential hyperplasia of the retinal epithelium, or adrenal adenomas may also be present in FAP, and this association has historically been designated Gardner syndrome.[15-18] Of note, desmoid tumors may inflict considerable morbidity and mortality with an estimated 10-year survival rate of 69%.[19,20]

The gene mutated in FAP and AFAP, adenomatous polyposis coli (*APC*), was identified in 1991 through linkage analysis and positional cloning on chromosome 5q21.[21-23] APC behaves as a tumor suppressor that inhibits Wnt signaling. APC is a key component of a protein complex that targets beta-catenin for degradation via GSK-3β-mediated phosphorylation. When APC is mutated, this interaction is impaired, resulting in excess beta-catenin and its translocation into the nucleus. In the nucleus, beta-catenin activates T-cell factor 4 to increase transcription of numerous growth-related genes.[24]

Distinctive phenotypic correlations exist for specific mutations in the *APC* gene (see Figure 2). More than 90% of mutations introduce a premature stop codon that results in a truncated protein.[25,26] Deletions are less common. Classic FAP is associated with mutations between codons 169 and 1393, with a particularly severe phenotype seen between codons 1250 and 1464.[27,28] AFAP typically correlates with mutations at the 5′ end, exon 9, and 3′ end.[29,30]

The genetic diagnosis of FAP/AFAP in at-risk families should begin with individuals demonstrating polyposis. Full gene sequencing of exons and exon-intron boundaries, and gene deletion analysis should be performed. Approximately 80% of individuals with features compatible with FAP will demonstrate a mutation.[31] If a mutation is found in the proband, other at-risk family members (particularly first-degree relatives) need only be tested for this specific mutation. In this setting, the absence of the family mutation in a relative at-risk can be considered a true negative. Fifteen percent to 20% of individuals with mutations will have no family history, suggesting a spontaneous germline mutation.[32] The diagnosis of *MUTYH*-associated polyposis should be considered in those who do not have an identifiable *APC* mutation.

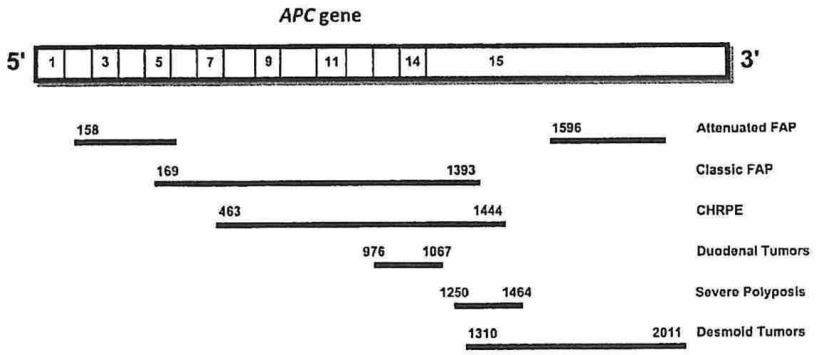

Figure 2. Genotype–phenotype correlations of mutations in the *APC* gene. A schematic representation of the 15 exons with mutations in the corresponding amino acid sequence and associated phenotype is illustrated.

Individuals with classic FAP should begin annual screening sigmoidoscopies at age 10 to 12 years. Once adenomas are detected, annual colonoscopies are reasonable. Prophylactic colectomy with either ileorectal anastomosis, ileal pouch-anal anastomosis, or ileostomy presently remains the only definitive therapy, and timing should be considered in the context of the number, size, and histology of polyps. In most patients, this is performed before the age of 25 years. Vigorous screening of any remaining rectum or the rectal cuff should be performed by sigmoidoscopy every 6 months.[33] At many centers, chemopreventive agents such as sulindac and celecoxib have been used in an adjunctive manner postoperatively. It is not clear what impact these agents have on the risk of colorectal, duodenal, or ampullary cancer.[34,35] Patients with AFAP should undergo annual screening colonoscopies beginning at age 25 years, or younger depending on family history. The decision for endoscopic management versus colectomy in AFAP patients will depend on the severity of the phenotype.

Given the high risk of duodenal or ampullary adenocarcinoma in FAP and AFAP patients, upper endoscopy with a forward and side-viewing endoscope should be performed prior to colectomy or by age 30.[36] Repeat examination should be performed in 1- to 5-year intervals depending on endoscopic findings and histology.[37,38] Regular thyroid ultrasounds beginning at the age of 12 years have been advocated by some groups. Serial alpha-fetoprotein (AFP) measurements and abdominal ultrasounds remain controversial for screening of childhood hepatoblastomas. Additional testing for other extracolonic malignancies may be warranted depending on family history or genotype.

MUTYH-Associated Polyposis

MUTYH-associated polyposis (MAP) represents the first described autosomal recessive colon cancer syndrome.[39] Patients with MAP may present similarly to AFAP patients, with an oligopolyposis phenotype. However, phenotypes that span a spectrum from no polyps to numbers similar to classical FAP have been described.[40-42] While the true incidence remains unknown, MAP may account for 0.5% to 1% of all colorectal cancers.[43] Biallelic mutations of the *MUTYH* (or *MYH*) gene were noted to be present in 22% to 29% of North Europeans with greater than 10 adenomatous polyps, as well as 28% of *APC* germline-negative patients with 10 to 100 polyps.[44-46] While the risk of developing colon cancer in MAP has not been rigorously defined, colorectal cancer cohort studies suggest a penetrance of 19% by age 50 and 43% by age 60.[47] Some have estimated the lifetime risk to be 80%.[48] The progression from polyposis to cancer may be shortened compared to AFAP given that approximately 60% of patients with MAP will have cancer diagnosed at the first presentation of polyposis.[49] Extracolonic manifestations similar to FAP/AFAP have been reported.[50,51] In particular, the risks of duodenal polyposis and duodenal cancer are estimated to be 17% and 4%, respectively.[51] Based on case control studies, the colon cancer risk in the heterozygote carrier appears to be slightly elevated and similar to an individual with a first-degree relative with colon cancer.[52]

The MUTYH protein is a base excision repair glycosylase involved in the repair of oxidative damage to guanine.[53] Bi-allelic germline mutations in the *MUTYH* gene result in G:C to T:A transversions, and frequently occur in coding regions of *APC*, as well as other genes such as *KRAS* and *BRCA1/2*.[40,54] Mutations in two hotspots, Y165C or G382D, account for 70% of all Caucasian mutations.[49] Genetic testing for these specific mutations is performed first, followed by full gene sequencing if negative. Individuals with greater than 10 adenomatous polyps (particularly with family history of colon cancer consistent with recessive inheritance) and significant polyposis similar to AFAP/FAP that test negative for mutations in *APC* should be tested for MAP. If a mutation is identified in the proband, siblings should be offered testing. A strategy to test spouses to clarify the risk in offspring would then be warranted.[55]

Screening should begin at age 18 to 20 years with colonoscopies performed every 1 to 2 years. Particular diligence should be applied to completely remove hyperplastic polyps and serrated adenomas, which can occur in MAP. Colectomy can be considered in cases where the polyp burden mimics FAP. Guidelines for the screening of duodenal cancers in FAP/AFAP should be applied to MAP patients as well.

Hyperplastic Polyposis Syndrome

While sporadic hyperplastic polyps in the rectum and sigmoid colon generally confer no malignant risk, patients with hyperplastic polyposis syndrome (HPS) demonstrate a high risk of developing colon cancer. Although not rigorously defined, small cohort studies have demonstrated a colon cancer prevalence of 35% to 54% in patients diagnosed with HPS.[56,57] Characterized by the development of numerous, proximal or large hyperplastic and sessile serrated polyps, HPS is estimated to arise in 1 in 2,000 individuals.[58] No germline mutation has yet been identified, and the pattern of inheritance remains unclear. World Health Organization criteria for HPS include the following: (1) $\geq$5 hyperplastic polyps proximal to the sigmoid colon (at least two of which are $\geq$1 cm in diameter), (2) a total of greater than 30 hyperplastic polyps, (3) or any hyperplastic polyp proximal to the sigmoid colon in a person with a first-degree relative who has HPS.[59] A small subset of individuals with multiple hyperplastic polyps carries bi-allelic *MUTYH* gene mutations, so genetic testing for MAP should be offered. No clear

management strategies or guidelines exist for HPS patients and their relatives. Some have recommended a repeat colonoscopy 1 year after the diagnosis, followed by surveillance every 1 to 3 years. First-degree relatives should be screened at age 40, or 10 years prior to the earliest age of diagnosis in the family. Prophylactic colectomy can be considered in cases with significant polyp burden that is not manageable endoscopically.

Peutz-Jeghers Syndrome

A rare autosomal dominant condition (1 in 150,000 persons), Peutz-Jeghers syndrome (PJS) is characterized by the development of pigmented macules on lips, buccal mucosa, hands, and feet. PJS also results in the development of hamartomatous polyps, benign polyps comprised of several types of epithelial cells supported by a thick band of smooth muscle, throughout the gastrointestinal tract (particularly the small bowel) that may cause bleeding, intussusception, or obstruction (Figure 3).[60] The lifetime risk of colon cancer is 39%, and 93% for any malignancy.[61] Other cancers include stomach, small bowel, pancreas, breast, sex cord, uterine, cervical, and melanoma.[62–68]

PJS has been associated with germline mutations or deletions in *LKB1* (*STK11*), a serine–threonine kinase that regulates p53-mediated apoptosis and the mammalian target of rapamycin (mTOR) pathway.[69,70] Only 50% to 60% of cases of suspected PJS have had mutations or deletions identified.[71] Criteria for a clinical diagnosis of PJS include (1) two or more PJS polyps in the gastrointestinal tract, (2) one or more PJS polyps with characteristic mucocutaneous pigmentation, or (3) one or more PJS polyp with a family history.[72] Positive genetic testing in an affected individual is helpful to guide testing in at-risk relatives. If no mutation is identified, first-degree relatives should have careful, regular physical examinations from birth for signs and symptoms.

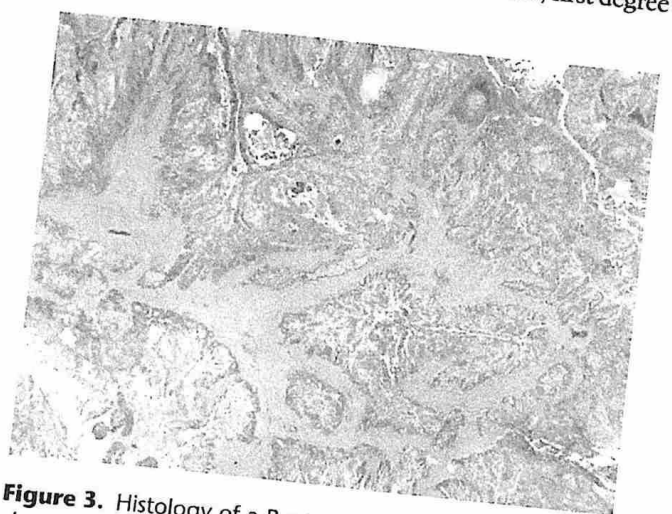

Figure 3. Histology of a Peutz-Jeghers Polyp. The polyp is characterized by glandular epithelium and a central core of arborizing smooth muscle contiguous with the muscularis mucosae. (Photo courtesy of Dr Mari Mino-Knudson, Massachusetts General Hospital Department of Pathology.)

Recommendations from the National Comprehensive Cancer Network (NCCN) for surveillance include upper endoscopy and small bowel imaging every 2 to 3 years starting at age 10 years, colonoscopy every 2 to 3 years from the late teens, magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound (EUS) with carcinoembryonic antigen (CA)19–9 measurement every 1 to 2 years from age 30 years, mammogram and breast magnetic resonance imaging annually with breast examinations twice per year from age 25 years, testicular examiantions for males from age 10 years, and annual Pap smears from age 18 years. The chemopreventive effect of COX-2 inhibitors and mTOR inhibitors for colon cancer remains under investigation.[73,74]

Juvenile Polyposis Syndrome

While sporadic juvenile polyps, a type of hamartomatous polyp, are relatively common in the pediatric population and carry little malignant potential, individuals with juvenile polyposis syndrome (JPS) present with multiple juvenile polyps throughout the gastrointestinal tract. Symptoms of bleeding, obstruction, and intussusception typically present during childhood. An autosomal dominant disorder, JPS confers a 10% to 38% lifetime risk of colon cancer with an average age of diagnosis at 34 years.[75–78] Moreover, patients also have a 15% to 21% lifetime risk of gastric and duodenal cancers.[75,76] Diagnostic criteria for JPS include the following: (1) more than three juvenile polyps in the colon, (2) any juvenile polyp outside of the colon, or (3) any juvenile polyp with a family history of JPS.

Mutations in genes related to the transforming growth factor-beta (TGF-β)/SMAD pathway have been associated with the development of JPS.[79] Germline mutations in *MADH4*, *BMPR1A*, and *ENG* thus far have been identified with direct sequencing commercially available. While mutations are predominantly found in *MADH4* and *BMPR1A*, only 40% to 50% of cases of JPS have identifiable mutations among these three genes.[80] Colonoscopy should be performed in JPS patients, or at-risk family members, beginning at age 15 years every 1 to 2 years. Upper endoscopy should be performed every 1 to 2 years after the age of 25 years.

NONPOLYPOSIS SYNDROMES

Lynch Syndrome

Lynch syndrome (or hereditary nonpolyposis colorectal cancer [HNPCC]) is the most common of the known hereditary colon cancer syndromes, responsible for 1% to 4% of all colon cancers and approximately 10% of cases before the age of 50 years.[4,81] Although the typical age of colon cancer diagnosis is reported to be in the 40s, some recent data indicate that the median age of colon cancer

diagnosis may be as high as 61 years, with a lifetime risk of 52% in women and 69% in men.[82] Transmitted in an autosomal dominant fashion, it commonly presents with only a few proximal adenomas that have a rapid progression to malignancy compared to adenomas occurring in the general population.[83] Extracolonic malignancies are also notable in Lynch syndrome; endometrial, gastric, ovarian, urinary collecting system, skin, pancreatic, and bile duct cancers also may develop.[84] Particularly striking, the lifetime risks of endometrial and ovarian cancer are estimated at 60% and 12%, respectively.[85] Turcot and Muir-Torre syndromes are variants of Lynch syndrome associated with glioblastomas and sebaceous skin tumors, respectively.[14,86]

Germline mutations in one of four DNA mismatch repair (MMR) genes have been typically associated with Lynch syndrome: *MSH2, MLH1, MSH6,* or *PMS2*.[87-94] These genes encode proteins that maintain the fidelity of short segments of nucleotide repeats, known as microsatellites. When mutated, MMR proteins are unable to repair bases that are incorrectly added to or deleted from microsatellites during DNA replication.[95] More recently, germline mutations in the gene, *EPCAM*, also have been linked to Lynch syndrome. While not a MMR gene itself, mutations in *EPCAM* result in hypermethylation of the *MSH2* promoter and loss of its expression. This microsatellite instability (MSI) results in a fertile field for the rapid accumulation of mutations in other growth regulatory genes. MSI is not unique to colon cancers from Lynch syndrome. Fifteen percent of sporadic colon cancers may exhibit MSI as a result of somatic hypermethylation of the *MLH1* promoter, and these tumors characteristically harbor somatic mutations in the serine/threonine kinase *BRAF*.[85,96,97] Sequencing of *BRAF* and *MLH1* hypermethylation assays may help determine whether a tumor with MSI is sporadic or associated with Lynch syndrome.[98,99]

Phenotypic correlations exist with mutations in specific MMR genes. *MLH1* mutations have been associated with an earlier age of presentation for colorectal carcinoma compared to *MSH2* (42.2 *v* 44.8 years).[100] Urinary tract and sebaceous gland skin tumors are more common among *MSH2* carriers.[101,102] A stronger association of endometrial cancer has been linked to *MSH6*.[103] *PMS2* carriers have been observed to demonstrate an older age of presentation for colorectal carcinoma and lower overall risk for colorectal carcinoma.[104,105]

The clinical diagnosis of Lynch syndrome has traditionally relied on the application of the Amsterdam I

Table 1. Clinical Guidelines for the Diagnosis of Lynch Syndrome

Amsterdam I criteria

At least three relatives with colorectal cancer including all of the following:

1) One should be a first degree relative of the other two
2) At least two successive generations be involved
3) At least one colorectal cancer case diagnosed before the age of 50 years
4) FAP should be excluded in any cases of colorectal cancer
5) Tumors should be verified by pathological examination

Amsterdam II criteria

Three relatives with a Lynch-associated cancer (colorectal, endometrial, small bowel, ureter, or renal pelvis) including all of the following:

1) One should be a first relative of the two
2) At least two successive generations should be involved
3) Cancer in one of the affected individuals should be diagnosed before the age of 50 years
4) FAP should be excluded in any cases of colorectal cancer
5) Tumors should be verified by pathological examination

Revised Bethesda guidelines

1) Colorectal cancer diagnosed in a patient who is less than 50 years of age
2) Synchronous, metachronous colorectal cancer, or other Lynch-related cancer* regardless of age
3) Colorectal cancer with MSI-H histology (presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern) diagnosed in a patient less than 60 years of age.
4) Colorectal cancer diagnosed in one or more first-degree relatives with a Lynch-related tumor*, with one of the cancers being diagnosed under age 50 years
5) Colorectal cancer diagnosed in two or more first- or second-degree relatives with Lynch-related tumors*, regardless of age

*Includes endometrial, ovarian, gastric, small bowel, urinary tract, biliary tract, pancreas, brain, and sebaceous gland.

Table 2. NCCN Guidelines for Extracolonic Cancer Surveillance in Lynch Syndrome

Gastric and duodenal cancer
- Upper gastrointestinal endoscopy with side-viewing examination at age 25–30 years with repeat examination in 1–3 years

Urothelial cancer
- Annual urinalysis

CNS cancers
- Annual physical examinations. No recommendations have been made

Pancreatic cancer
- Annual physical examination. No recommendations have been made

Endometrial and ovarian cancer
- Patient education and response to endometrial cancer symptoms
- Referral to gynecologic oncologist for surveillance (annual endometrial sampling, transvaginal ultrasound, and serial CA-125 measurements starting by age 30–35 years or 5–10 years before the earliest age in the family)
- Consider prophylactic total abdominal hysterectomy and salpingo-oophrectomy after completion of childbearing or during colectomy

criteria (see Table 1).[106] Since its development in 1991, it has a reported sensitivity of only 60% and specificity of 70%.[107-109] Amsterdam II criteria (see Table 1) were developed in 1999 to include extracolonic malignancies with the goal of increasing sensitivity.[110] However, several studies have demonstrated that the overall performance still remains too restrictive.[111] A broader set of criteria known as the revised Bethesda guidelines (see Table 1) were developed to determine which colonic tumors should undergo MSI analysis and immunohistochemistry.[112] Given the increased availability of DNA sequencing, a formal diagnosis of Lynch syndrome should ultimately be based on mutational analysis of MMR genes.

For individuals that satisfy Amsterdam criteria, direct gene sequencing of Lynch-associated genes should be pursued. If a mutation is identified, at-risk first-degree relatives may be tested specifically for the particular gene. Patients that meet only the Bethesda guidelines should first have their tumors assessed for MSI and/or MMR protein staining by immunohistochemistry (IHC), followed by gene sequencing if positive. Interpreting test results is a challenge if a tumor exhibits MSI or absent IHC staining but no germline mutation is identified. If the MLH1 protein specifically is absent on IHC, hypermethylation analysis of *MLH1* and *BRAF* mutation testing can be performed to establish the sporadic nature of the tumor. However, if tumors do not exhibit MSI and no mutation is found, these families are unlikely to represent Lynch kindreds and have been tentatively designated as "syndrome X."

Broader use of MSI and/or IHC testing of colonic tumors has been adopted by many institutions to capture additional individuals with Lynch syndrome that would be missed by current guidelines. Universal screening and use of mathematical prediction models have been proposed by some centers.[113] Given the observation that MSI-high tumors display less aggressive behavior, as well as that MSI tumors respond poorly to 5-fluorouracil–based chemotherapy, MSI testing for stage II colon cancers is becoming more routine.[114]

For surveillance, colonoscopy should be performed every 1 to 2 years beginning at age 20 to 25 years or 10 years earlier than the earliest colon cancer in the family. Annual colonoscopies should begin after age 40 years.[115] Given the high rate of metachronous tumors, individuals with Lynch syndrome and colon cancer should be advised to pursue a subtotal colectomy with ileorectal anastomosis. Surveillance of the remaining rectum should be performed on an annual basis.[116]

The impact of screening for extracolonic tumors in Lynch syndrome on mortality remains unknown, and is generally personalized to the family history. Endometrial cancer screening has been recommended beginning from age 30 to 35 years for all women, with consideration of prophylactic total abdominal hysterectomy and bilateral salpingo-oopherectomy (TAH-BSO) after completion of childbirth.[117] Urinalysis and cytology have been used by some centers beginning at age 20 to 25 years. Recommendations from the NCCN are summarized in Table 2. Cancer surveillance is less intensive and limited to colonoscopy in patients with syndrome X.

CONCLUSION

Diagnosis and management of hereditary colon cancers requires a concerted effort by practitioners to integrate an array of data from personal and family

history, physical examination, endoscopy, and genetic analyses. The care of individuals and families with hereditary colon cancer is distinctly different from those with sporadic cancers, and the association of extracolonic malignancies requires careful coordination among numerous specialists. As the utilization of genomic sequencing and genome-wide association studies grows, the discovery of additional genetic mechanisms will hopefully translate into new opportunities for diagnosis and management. Identification of novel genes, modifiers, and detailed genotype-phenotype correlations holds the promise of more effective and tailored screening and surveillance approaches for these syndromes.

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ELENCO N. 2

- Sindrome di Gardner e Turcot: implicazioni diagnostico e terapeutiche

- Quali software utilizzerebbe per la costruzione di un Database di ricerca?

Hereditary Colon Cancer Syndromes

Manish Gala and Daniel C. Chung

Colon cancer is associated with a family history in up to 25% of cases. As many as 5% are associated with an established hereditary syndrome, demonstrating the profound influence of inheritable genetic mechanisms in the development of this disease. These syndromes confer a diverse spectrum of risk, age of presentation, endoscopic and histological findings, extracolonic manifestations, and modes of inheritance. As the molecular characteristics of these disorders become better described, enhanced genotype-phenotype correlations may offer a more targeted approach to diagnosis, screening, and surveillance. While the strategies for diagnosis and management of familial adenomatous polyposis (FAP) and Lynch syndrome are more established, the approach to newly recognized syndromes such as *MUTYH*-associated polyposis (MAP) and hyperplastic polyposis syndromes continues to evolve. Effective cancer prevention in affected individuals and at-risk family members first requires timely recognition of these hereditary colon cancer syndromes followed by integration of genetic testing and clinical examinations.
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Colorectal cancer remains the third most common cancer diagnosed among men and women in the United States, with 142,570 new cases projected to occur in 2010.[1] Despite a reduction in the age-adjusted incidence rate from 54.4 to 45.5 per 100,000 persons between 2000 and 2007, an estimated 51,370 deaths are expected to occur in 2010, accounting for approximately 9% of all cancer deaths.[1,2] In addition to lifestyle modifiers, genetic risk factors are known to play a significant role in the development of colon cancer. While as many as 25% of cases are associated with a family history of the disease, 5% of cases develop in the setting of an established familial genetic syndrome.[3,4] As the catalogue of inheritable genetic mechanisms expands, the ability of healthcare providers to identify such patients and affected family members for appropriate counseling, screening, and surveillance will be critical for effective cancer prevention and management.

Recognition of hereditary colon cancer syndromes first requires the raised suspicion of the thoughtful clinician. In addition to a carefully documented family history, age of presentation, personal and family history of extracolonic tumors, endoscopic findings, and physical examiantion findings can be important clues to establishing a diagnosis. Frequently divided into nonpolyposis or polyposis colon cancer syndromes, we will discuss the salient features and management strategies for these disorders.

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POLYPOSIS SYNDROMES

Familial Adenomatous Polyposis/Attenuated Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is the most common polyposis syndrome, with a prevalence of one in 5,000-7,000 persons.[5] Characterized by the progressive development of hundreds to thousands of adenomatous colonic polyps beginning in the second decade of life, it carries a 100% percent risk of colorectal cancer (see Figure 1). Compared to the median age of diagnosis of 70 years for sporadic cases, colon cancer develops in patients with FAP at 40 years, or 10 to 15 years after the initial development of polyposis.[2] Transmitted in an autosomal dominant fashion, FAP exhibits 100% penetrance among affected individuals.

Attenuated adenomatous polyposis (AFAP) typically presents with an oligopolyposis of less than 100 adenomas with a right-sided predominance and flat morphology.[6] The lifetime risk of colorectal cancer is not as inevitable as with FAP, but it is still estimated to be up to 69%. The median ages of onset of polyposis and colorectal cancer are 35-45 years and 55 years, respectively.[7] This delay in presentation and reduced polyp number compared to classic FAP can make the diagno-

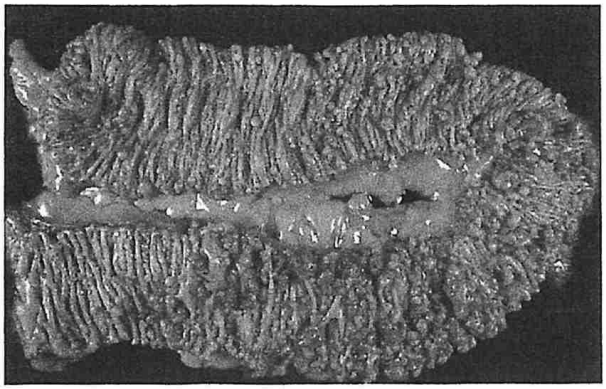

Figure 1. Gross pathology specimen from a FAP patient undergoing total colectomy. The colon is carpeted with hundreds to thousands of adenomatous polyps. (Photo courtesy of Dr Mari Mino-Knudson, Massachusetts General Hospital Department of Pathology.)

sis difficult. Genetic testing may be required to differentiate AFAP from sporadic cancers and other syndromes such as Lynch.[8]

There are several important extracolonic manifestations associated with FAP/AFAP. More than 90% of patients with FAP will develop duodenal, ampullary, or peri-ampullary adenomas, with 5% to 10% of patients developing duodenal carcinoma by age 60.[9,10] Fundic gland polyps and antral adenomas are also quite common and are usually benign. The risk of gastric adenocarcinoma is less than 1% in Western populations.[11] The risks of upper intestinal lesions are similar for AFAP.[8] Other extracolonic cancers include follicular and papillary thyroid cancers, which may precede the development of polyposis and present in up to 12% of patients.[12] Hepatoblastoma has been observed in a subset of young children.[13] Turcot syndrome, the presence of CNS tumors with a hereditary colon cancer syndrome, can present with medulloblastomas, and less commonly with gliomas.[14] Benign growths such as desmoids, osteomas, supernumerary teeth, epidermoid cysts, congential hyperplasia of the retinal epithelium, or adrenal adenomas may also be present in FAP, and this association has historically been designated Gardner syndrome.[15-18] Of note, desmoid tumors may inflict considerable morbidity and mortality with an estimated 10-year survival rate of 69%.[19,20]

The gene mutated in FAP and AFAP, adenomatous polyposis coli (*APC*), was identified in 1991 through linkage analysis and positional cloning on chromosome 5q21.[21-23] APC behaves as a tumor suppressor that inhibits Wnt signaling. APC is a key component of a protein complex that targets beta-catenin for degradation via GSK-3β-mediated phosphorylation. When APC is mutated, this interaction is impaired, resulting in excess beta-catenin and its translocation into the nucleus. In the nucleus, beta-catenin activates T-cell factor 4 to increase transcription of numerous growth-related genes.[24]

Distinctive phenotypic correlations exist for specific mutations in the *APC* gene (see Figure 2). More than 90% of mutations introduce a premature stop codon that results in a truncated protein.[25,26] Deletions are less common. Classic FAP is associated with mutations between codons 169 and 1393, with a particularly severe phenotype seen between codons 1250 and 1464.[27,28] AFAP typically correlates with mutations at the 5′ end, exon 9, and 3′ end.[29,30]

The genetic diagnosis of FAP/AFAP in at-risk families should begin with individuals demonstrating polyposis. Full gene sequencing of exons and exon–intron boundaries, and gene deletion analysis should be performed. Approximately 80% of individuals with features compatible with FAP will demonstrate a mutation.[31] If a mutation is found in the proband, other at-risk family members (particularly first-degree relatives) need only be tested for this specific mutation. In this setting, the absence of the family mutation in a relative at-risk can be considered a true negative. Fifteen percent to 20% of individuals with mutations will have no family history, suggesting a spontaneous germline mutation.[32] The diagnosis of *MUTYH*-associated polyposis should be considered in those who do not have an identifiable *APC* mutation.

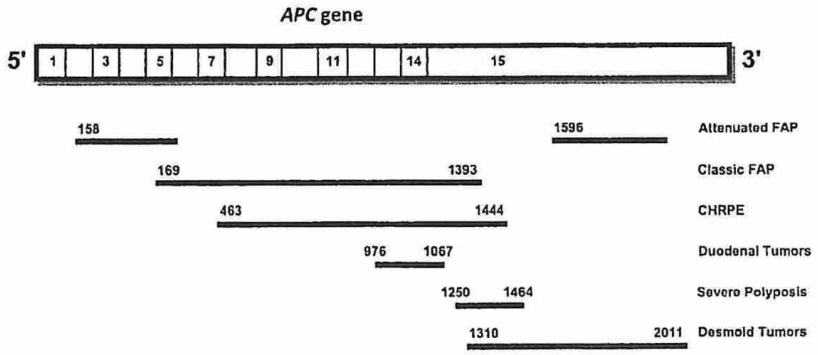

Figure 2. Genotype–phenotype correlations of mutations in the *APC* gene. A schematic representation of the 15 exons with mutations in the corresponding amino acid sequence and associated phenotype is illustrated.

Individuals with classic FAP should begin annual screening sigmoidoscopies at age 10 to 12 years. Once adenomas are detected, annual colonoscopies are reasonable. Prophylactic colectomy with either ileorectal anastomosis, ileal pouch-anal anastomosis, or ileostomy presently remains the only definitive therapy, and timing should be considered in the context of the number, size, and histology of polyps. In most patients, this is performed before the age of 25 years. Vigorous screening of any remaining rectum or the rectal cuff should be performed by sigmoidoscopy every 6 months.[33] At many centers, chemopreventive agents such as sulindac and celecoxib have been used in an adjunctive manner postoperatively. It is not clear what impact these agents have on the risk of colorectal, duodenal, or ampullary cancer.[34,35] Patients with AFAP should undergo annual screening colonoscopies beginning at age 25 years, or younger depending on family history. The decision for endoscopic management versus colectomy in AFAP patients will depend on the severity of the phenotype.

Given the high risk of duodenal or ampullary adenocarcinoma in FAP and AFAP patients, upper endoscopy with a forward and side-viewing endoscope should be performed prior to colectomy or by age 30.[36] Repeat examination should be performed in 1- to 5-year intervals depending on endoscopic findings and histology.[37,38] Regular thyroid ultrasounds beginning at the age of 12 years have been advocated by some groups. Serial alpha-fetoprotein (AFP) measurements and abdominal ultrasounds remain controversial for screening of childhood hepatoblastomas. Additional testing for other extracolonic malignancies may be warranted depending on family history or genotype.

MUTYH-Associated Polyposis

MUTYH-associated polyposis (MAP) represents the first described autosomal recessive colon cancer syndrome.[39] Patients with MAP may present similarly to AFAP patients, with an oligopolyposis phenotype. However, phenotypes that span a spectrum from no polyps to numbers similar to classical FAP have been described.[40-42] While the true incidence remains unknown, MAP may account for 0.5% to 1% of all colorectal cancers.[43] Biallelic mutations of the *MUTYH* (or *MYH*) gene were noted to be present in 22% to 29% of North Europeans with greater than 10 adenomatous polyps, as well as 28% of *APC* germline-negative patients with 10 to 100 polyps.[44-46] While the risk of developing colon cancer in MAP has not been rigorously defined, colorectal cancer cohort studies suggest a penetrance of 19% by age 50 and 43% by age 60.[47] Some have estimated the lifetime risk to be 80%.[48] The progression from polyposis to cancer may be shortened compared to AFAP given that approximately 60% of patients with MAP will have cancer diagnosed at the first presentation of polyposis.[49] Extracolonic manifestations similar to FAP/AFAP have been reported.[50,51] In particular, the risks of duodenal polyposis and duodenal cancer are estimated to be 17% and 4%, respectively.[51] Based on case control studies, the colon cancer risk in the heterozygote carrier appears to be slightly elevated and similar to an individual with a first-degree relative with colon cancer.[52]

The MUTYH protein is a base excision repair glycosylase involved in the repair of oxidative damage to guanine.[53] Bi-allelic germline mutations in the *MUTYH* gene result in G:C to T:A transversions, and frequently occur in coding regions of *APC*, as well as other genes such as *KRAS* and *BRCA1/2*.[40,54] Mutations in two hotspots, Y165C or G382D, account for 70% of all Caucasian mutations.[49] Genetic testing for these specific mutations is performed first, followed by full gene sequencing if negative. Individuals with greater than 10 adenomatous polyps (particularly with family history of colon cancer consistent with recessive inheritance) and significant polyposis similar to AFAP/FAP that test negative for mutations in *APC* should be tested for MAP. If a mutation is identified in the proband, siblings should be offered testing. A strategy to test spouses to clarify the risk in offspring would then be warranted.[55]

Screening should begin at age 18 to 20 years with colonoscopies performed every 1 to 2 years. Particular diligence should be applied to completely remove hyperplastic polyps and serrated adenomas, which can occur in MAP. Colectomy can be considered in cases where the polyp burden mimics FAP. Guidelines for the screening of duodenal cancers in FAP/AFAP should be applied to MAP patients as well.

Hyperplastic Polyposis Syndrome

While sporadic hyperplastic polyps in the rectum and sigmoid colon generally confer no malignant risk, patients with hyperplastic polyposis syndrome (HPS) demonstrate a high risk of developing colon cancer. Although not rigorously defined, small cohort studies have demonstrated a colon cancer prevalence of 35% to 54% in patients diagnosed with HPS.[56,57] Characterized by the development of numerous, proximal or large hyperplastic and sessile serrated polyps, HPS is estimated to arise in 1 in 2,000 individuals.[58] No germline mutation has yet been identified, and the pattern of inheritance remains unclear. World Health Organization criteria for HPS include the following: (1) $\geq$5 hyperplastic polyps proximal to the sigmoid colon (at least two of which are $\geq$1 cm in diameter), (2) a total of greater than 30 hyperplastic polyps, (3) or any hyperplastic polyp proximal to the sigmoid colon in a person with a first-degree relative who has HPS.[59] A small subset of individuals with multiple hyperplastic polyps carries bi-allelic *MUTYH* gene mutations, so genetic testing for MAP should be offered. No clear

ELENCO N. 3

- Valutazione del rischio di malignità nell'adenomaepatocellulare

- Quali motori di ricerca utilizzerebbe per la costruzione di una review sistematica/metanalisi su un argomento scientifico?

ELENCO N. 4

- Valutazione della risposta al trattamento del cancro colon-rettale.

- Come costruirebbe un Database su Excel?