Genetics of Young Onset Colorectal Cancer

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

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


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

Lynch syndrome (LS) and familial adenomatous polyposis (FAP) are the most common of the hereditary CRC syndromes so far described, with a well-defined genetic basis. This review focuses on the genetic basis of the major young-onset CRC syndromes, as well as the rarer genetic syndromes with a predisposition for young-onset CRC, including the PTEN hamartoma syndromes and hereditary mixed polyposis syndromes. We also cover rare, low-penetrance genetic loci thought to confer an increased risk for young-onset CRC, but for which conclusive evidence is still lacking (Figure I and Table 1).

Lynch Syndrome

Overview

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

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

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

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


**Genetics**

LS are caused by germline mutations in one of four DNA MMR genes (MMR), MLH1, MSH2, PMS2 and MSH6. These DNA MMR genes maintain genomic stability by correcting nucleotide mismatches that occur during DNA replication. Microsatellites are mono, di- and tri-nucleotide repeats spread throughout the genome and these nucleotide repeats may be amplified when the DNA MMR system is inactivated, leading to microsatellite instability (MSI). MSI occurs in individuals with LS when a second somatic mutation in the affected tissue inactivates the function of DNA MMR. MSI measured in the tumor represents an increased number of mono-, di-, or tri-nucleotide repeats in the tumor compared to the normal tissue. MSI itself may occur in genes important for the repair of DNA mismatches.

MSI is subclassified by the number of microsatellite markers showing instability. Tumors expressing MSI in two or more markers from the National Cancer Institute (BAT26, BAT25, DSS346, D2S123 and D17S250) are termed MSI-high while those with only one marker are termed MSI-low. MS-stable or MSS tumors have no microsatellite instability. MSI itself may occur in genes important for the repair of DNA mismatches.
to cell cycle and growth regulation, creating a mutator phenotype that may result in cancer. MSI is a feature of LS-associated cancers and is present in 85-90% of LS-associated CRC. Somatic hypermethylation of the MLH1 promoter region may inactivate MLH1 and accounts for as many as 15-25% MSI-positive sporadic CRC [9]. Up to 90% of all LS cases have been attributed to germline mutations in MLH1 or MSH2, but this may be an overestimate since mutations in MLH6 and PMS2 may have a more attenuated phenotype and thus be underdiagnosed [13,17]. On universal screening of 1,066 CRC, 23 cases were diagnosed with LS, with 13% and 9% attributable to an MSH6 or a PMS2 mutation respectively [18]. Moreover, there appears to be geographic difference in MMR mutations. For example, in Finland, MLH1 mutations accounted for 83% of the mutations, with MSH2 mutations only accounting for 3% [19].

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

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

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

Genetic testing

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

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

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

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

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

Familial Colorectal Cancer X

Overview

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

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

Overview

Constitutional DNA mismatch repair deficiency (CMMRD) is the result of germline biallelic mutations in DNA MMR genes. CMMRD predisposes to a much earlier age of onset of CRC than LS with an average age of 16 years (range 8-35 years) at CRC diagnosis [37-40]. Since the first report of homozygous MMR mutation in 1999, familial cases have been described and the constellation of observed malignancies have been termed constitutional mismatch repair disorder (CMMRD) [37,41]. CMMRD typically manifests in the first decade as a spectrum of malignancies, particularly hematological and central nervous system cancers and with café au lait spots (CALS) reminiscent of neurofibromatosis type 1 (NF-1) [41]. LS-associated malignancies,
notably, CRC and small bowel adenocarcinomas may follow the initial malignancies [42]. Adenomatous polyps are also frequently discovered, often at the time of CRC diagnosis [43].

Genetics

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

Genetic testing

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

FAP

Overview

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

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

Genetics of FAP

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

Genetic testing

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

MutYH-associated polyposis

Overview

MutYH-associated polyposis (MAP) was first described in 2002, in a family suffering from adenomatous polyposis despite testing negative for a germline APC mutation [61]. Mutations in the human analog of E. coli mutY gene, and more of the FAP patients have a detectable mutation and only 10-30% of MAP-related CRCs show a predilection for the right side and a 100% and is by far the most common mutation detected in carriers [13]. However, the 11307K APC polymorphism, particularly prevalent amongst Ashkenazi Jews, approaches a low to moderate penetrance of 10 to 20% [53,54]. As such, more than a thousand variants of APC mutations have been described that produce a dysfunctional, truncated protein, a result of frameshift mutations or premature stop codons [55]. Individuals with APAF have mutation arising from APC mutations at the 5' or 3' ends of the gene or in certain areas of exon 9 [56]. APAF is also inherited in an autosomal dominant manner. An estimated 80% and more of the APAF patients have a detectable mutation and only 10-30% in the case of APAF [26]. In the remaining patients, a mutation in the MUYH gene should be considered [57-59].

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

Genetics

MYH encodes a DNA glycosylase participating in base-repair excision, with the principal function of protecting genomic information from reactive oxidative stress. Loss of MYH leaves DNA vulnerable to 7,8-dihydro-8-oxo-2-deoxyguanosine (8-oxoG), a highly deleterious by-product of oxidative DNA damage. 8-oxoG mispairs with adenine residues, leading to a high frequency of G:C to T:A transversions [73]. These transversions result in a nonsense or splice site mutations in APC and KRAS genes, leading the stage for uncontrolled cellular proliferation [55,74]. The acquired APC mutation in MAP explains the phenotypic similarities with FAP.

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

Genetic testing

Due to the phenotypic similarity between MAP and FAP/FAP, recommendations have been made that genetic testing for MYH mutations be performed on all polyposis patients without a clear pattern of inheritance and no detectable APC mutations [62]. Patients without polyposis testing negative for MMR mutations should also benefit from MYH testing, as the differential is extended to include the non-polyposis phenotype of MAP. Genetic testing first screens for the two most common variants found in individuals of Western European ancestry, Y165C and G383D. If a mutation is detected, the opposite allele is also tested. In the case of patients of non-Western European ancestry or if both variants test negative and a strong clinical suspicion of MAP remains, other less frequent variants are tested. Siblings of biallelic carriers have the highest risk (25%) of carrying biallelic mutations and should also be offered genetic testing.

Hamartomatous Polyposis Syndromes

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

Peutz Jeghers Syndrome (PJS)

Overview

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

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

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

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

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

Genetics of PJS

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

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

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

Juvenile Polyposis Syndrome (JPS)

Overview

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

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

Genetics

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

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

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

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

Genetic testing

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

PTEN Hamartoma Syndromes

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

Cowden syndrome

Overview: Cowden Syndrome (CS), alternatively known as Cowden’s Disease or Multiple Hamartoma Disease, is an autosomal dominant disorder first documented in 1963 by Lloyd and Denis [115]. It is part of the PTHS and is phenotypically diverse, presenting with macrocephaly, CNS lesions, multiple hamartomata and an increased...
risk of both benign and malignant tumors. The incidence of CS is estimated to be between 1 in 200,000 to 250,000 [116]. However, the actual prevalence is likely higher, as many of the features of CS are commonly found within the general population, leaving CS grossly underdiagnosed. CS is characterized by multi-organ hamartomatous growths, mostly manifesting in the gastrointestinal tract (71% of patients) and the skin and mucous membranes. Mucocutaneous hamartomas are among the most pathognomonic of CS, with patients presenting with trichilemmomas (hamartoma of the hair follicle infundibulum) and also with papilomatous papules and acral and plantar keratoses [Hobert, 2009 #666]. The esophagus and colon are the most frequently affected gastrointestinal regions. Polyp prevalence in CS varies and numbers as high as 93% have been reported [117,118]. CS has variable polyph histology- adenomatous, inflammatory, hyperplastic, lymphoid, ganglioneuromatous and leiomyomatous polyps have all been reported [119]. CS polyps have the distinct characteristic of containing neural elements. Patients with CS also have a known predisposition to thyroid, breast and endometrial cancers [120]. The dogma was one that traditionally excluded any CRC risk in CS patients and has since been proven wrong.

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

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

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

Bannayan-Ruvalcaba-Riley Syndrome

Overview

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

Genetics

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

Genetic testing

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

Hereditary Mixed Polyposis Syndrome (HMPS)

Overview

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

Genetics

The genetic locus for HMPS, CRAC1, was originally mapped to chromosome 6q, but was later found to be on chromosome 15q13-q21 [133,134]. The underlying genetic basis was recently characterized as a heterozygous duplication on chromosome 15q13-q21 upstream of GREM1, a gene involved in the BMP pathway, possibly explaining
the phenotypic overlap with JPS [135]. So far, GREM1 mutations have only been detected in Ashkenazi Jews who appear to share a common ancestry [135].

Genetic testing

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

Serrated Polyposis Syndrome (SPS)

Overview

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

Genetics

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

Genetic testing

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

Genetic Susceptibility Loci in Young Onset Colorectal Cancer

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

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

References


Jackson CC, Gallinger Pouchet CJ, W Kastrinos Peltomäki 17: 405-415.


day of human genetics 65: 1291-1298.


