Commentary (Burt): Genetics of Colorectal Cancer

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Approximately 6% of colorectal cancers can be attributed to recognizable heritable germline mutations. Familial adenomatous polyposis is an autosomal dominant syndrome classically presenting with hundreds to thousands of adenomatous colorectal polyps that are caused by mutations in the APC gene.

Colorectal cancer is undoubtedly one of the most genetically studied malignancies. In the past 20 years, substantial progress has been made in understanding the genetic and molecular pathogenesis of this cancer. It is instructive that the genes involved in the inherited colon cancer syndromes are the same genes involved in the etiology of most colorectal cancers. Familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome) arise from mutations of the adenomatous polyposis coli (APC) gene and mismatch repair genes, respectively. Approximately 80% of sporadic colorectal cancers begin with APC mutations, while another 15% have a mismatch repair mutation occurring early in their pathogenesis. Additional mutations in different genes accumulate as polyps progress in both size and histopathology to colon cancer.

The genes mutated in tumors harboring APC mutations are said to be a part of the chromosomal instability pathway. This name is given because loss-of-heterozygosity changes are frequently found in the DNA of tumor tissue. Involved genes include K-ras and p53 among others. Tumors with mismatch repair mutations almost always exhibit microsatellite instability (MSI). Additional mutations in such tumors include TGF-beta, BAX, and others, and this mutation pathway is appropriately called the MSI pathway.

This review, which may not be apparent from the title, exclusively addresses the inherited syndromes of colorectal cancer, including their genetic etiologies, phenotypes, and relevant approaches to genetic testing and management. FAP and HNPCC are covered in most detail with appropriate attention given to the hamartomatous polyposis conditions, juvenile polyposis, and Peutz-Jeghers syndrome. The review is reasonably complete, very instructive, and of substantial interest to the practicing oncology specialist who must frequently deal with such syndromes and their diagnosis. The authors raise a number of issues in the review that are worthy of further comment.

`Flat Adenoma` Syndrome
The authors mention that attenuated FAP is also known as “the hereditary flat adenoma syndrome.” This connotation was derived from the observation of multiple small adenomas in the proximal colon of several families with an inherited predisposition to colorectal cancer. After it was determined that attenuated FAP arose from APC mutations, these “flat adenoma” families were found to actually be attenuated FAP families. Furthermore, the small adenomas in such families were not histologically consistent with the “flat adenoma” originally described by Morrison at the St. Marks Hospital in London, but instead were typical small adenomas. Thus, it would seem appropriate to discontinue reference to the hereditary flat adenoma syndrome in favor of attenuated FAP.[1]

Gardner Syndrome
The authors note that FAP is a more commonly used term than Gardner syndrome. The designation Gardner syndrome came from descriptions by Eldon Gardner, PHD, of a family that exhibited colonic adenomatous polyposis typical of FAP, but also certain benign extraintestinal growths including osteoma and certain soft-tissue tumors, epidermoid cysts, and fibroma. It was not known at the time whether FAP and Gardner syndrome were genetically related.

Over time, additional extracolonic growths were added to the description of Gardner syndrome, including supernumerary teeth, desmoid tumors, adrenal adenomas, jaw bone opacities, odontomas, congenital hypertrophy of the retinal pigment epithelium (CHRPE), gastric fundic gland polyps, and duodenal adenoma. It became a semantic problem to decide whether only the syndrome seen in families with no extracolonic lesions should be called FAP, while all others should be called Gardner syndrome. Various combinations of lesions were evaluated in an attempt to determine if certain
groupings could reliably separate the conditions. Shortly after APC gene mutations were identified as the cause of FAP, it was determined that mutations in the same gene caused Gardner syndrome. Furthermore, identical lesions in that gene could give rise to both FAP and Gardner syndrome phenotypes. It seemed as though Gardner syndrome would quickly become relegated to the category of historical terms. Then a number of “genotype-phenotype” correlations were made for lesions related to Gardner syndrome. For example, CHRPE lesions were found only when the APC mutations were between exon 9 and the middle portion of exon 15, and osteomas, fibromas, and desmoids were more common with mutations in the distal areas of the gene. Continued work has revealed no clear-cut phenotype or genotype that consistently separates FAP and Gardner syndrome. Instead, the extracolonic findings individually relate to some degree to the mutation location in the APC gene. Nonetheless, the term Gardner syndrome persists and is often applied to families when extraintestinal features, particularly osteoma and soft-tissue growths, are a predominant part of the phenotype.

**Fundic Gland Polyps**

It is now generally agreed that gastric cancer, although unusual in FAP (about 0.5% lifetime risk), can indeed arise from fundic gland polyps [3]. These polyps likely develop dysplastic changes, sometimes leading to cancer. They can be a difficult management issue, as up to 30% of FAP patients diagnosed with the polyps exhibit some dysplastic change in them. Total gastrectomy seems to be the only sure treatment. In view of the morbidity of this procedure, however, it would seem inappropriate for most cases, considering the low risk of gastric cancer in FAP overall. On the other hand, the appearance of severe dysplasia should alert the clinician to consider intervention, possibly surgery.

Fundic gland polyps seem to occur in attenuated FAP with the same prevalence and phenotype as in typical FAP, although systematic study is needed. Interestingly, similar cases have been described in MYH-associated polyposis.

**APC Mutation Detection**

The authors refer to a frequently cited estimate of 90% to 95% as the deleterious mutation detection rate in the index case of families with clinically typical FAP. Recent work suggests that the rate is actually only 50% to 70%. A few cases in which no APC mutation is found will exhibit pathogenic MYH gene mutations, but most remain unexplained. As the authors stress, once a deleterious mutation is found in the index case, other family members can be tested with mutation-specific testing with nearly 100% accuracy.

**Lynch Syndrome and Genetic Testing**

The authors carefully explain how the clinician determines who should undergo genetic testing for Lynch syndrome and how to go about that testing. Several points are worth emphasizing. First, MSI and immunohistochemistry (IHC) testing of tumor tissue are not only of use in determining who should have “mutation finding” genetic testing, but they are also helpful—particularly in combination—in ruling out Lynch syndrome. Almost all colorectal cancers associated with HNPCC will exhibit MSI, with the exception of some cases related to MSH6 mutations. Thus, if a colon cancer does not exhibit MSI and there is expression of all mismatch repair genes by IHC, Lynch syndrome is effectively ruled out. As this approach remains imperfect, however, genetic testing probably should still be done in families meeting Amsterdam criteria.

Colonic adenomas do not reliably exhibit MSI in Lynch syndrome, although “advance adenomas”—ie, those that are larger than 1 cm in diameter or exhibit villous or advanced histology—often do. Other HNPCC cancers are likewise inconsistent in their expression of MSI.

A second point concerns the clinical implications of a family meeting Amsterdam criteria, but with no mutations found by genetic testing, negative MSI results, and unrevealing IHC. Such families are often still thought to exhibit Lynch syndrome because they meet the Amsterdam criteria. Three groups (including ours, and one quoted by the authors) have now demonstrated that such families do not develop an excess of the extracolonic cancers found in HNPCC. Even the colon cancer phenotype, in terms of age of onset and risk to relatives, is less severe than that seen in Lynch syndrome families where a mutation has been found.

Third, as also mentioned in the review, the pathogenesis of up to 30% of colon cancers appears to include inheritance. A number of groups are searching for the susceptibility genes in this setting—genes that appear to be less penetrant and result in a less severe phenotype than that observed in Lynch syndrome. Such families probably should undergo less aggressive screening than those who are genetically defined as having HNPCC, but more aggressive screening than the average-risk population.

The presently recommended screening strategy for persons in a family with multiple cases of colon cancer and an at-risk family member is a colonoscopy every 1–2 years, starting at age 20, and including excision of any adenomatous polyps detected. The authors note that adherence to this approach is often low.历史上，加德纳综合征似乎很快被归类为历史术语。然而，一些“基因型-表型”关联被用于涉及加德纳综合征的病变。例如，CHRPE病变仅在APC突变位于外显子9和中间部分的外显子15时出现，而骨瘤、纤维瘤和纤维瘤在基因的远端区域发生突变更为常见。持续的研究表明，APC基因的突变位置无清晰的肿瘤类型分离。相反，额外的病变在一定程度上与其所在基因的突变位置相关。然而，加德纳综合征的术语仍然存在，并且当外显病变作为主要表型时，通常应用于家族。**胃窦息肉**

目前普遍认为，虽然在FAP中胃癌的终生风险约为0.5%，但胃窦息肉确实可以导致胃癌[3]。这些息肉可能发展为不典型病变，有时导致癌症。全胃切除术似乎是唯一可靠的治疗方法。然而，考虑到FAP胃癌的整体风险，这种方法似乎不适用于大多数情况。另一方面，严重不典型病变的出现应引起临床医生的注意，考虑治疗，可能包括手术。

胃窦息肉在部分性FAP中也以相同的频率和表型出现，尽管需要系统的研究。有趣的是，在MYH相关的息肉疾病中也描述了类似的情况。

**APC突变检测**

作者引用了经常引用的90%至95%的致病性突变检测率在典型FAP家族中的病例。最近的研究表明，该比率实际上仅为50%至70%。少数APC突变未发现的病例将表现为MYH基因突变，但大多数仍不清楚。作者强调，一旦在索引病例中检测到致病性突变，其他家庭成员可以进行特异性突变检测，准确性几乎为100%。

**Lynch综合征和基因检测**

作者详细解释了如何确定应进行遗传检测的Lynch综合征患者以及如何进行检测。有几个要点值得强调。首先，MSI和免疫组织化学（IHC）检测肿瘤组织不仅用于确定应进行“发现突变”遗传检测的患者，而且在结合使用时特别有助于排除Lynch综合征。几乎所有的HNPCC相关结肠癌将表现出MSI，但有一些病例相关的MSH6突变除外。因此，如果一个结肠癌不表现出MSI，且所有错配修复基因的表达未被IHC揭示，Lynch综合征被认为已经有效排除。尽管这种方法仍不完美，遗传检测可能仍然应该在符合Amsterdam标准的家庭中进行。

结肠腺瘤在Lynch综合征中不一定会表现出MSI，尽管“进展性腺瘤”——即直径大于1 cm或具有 villous或不典型病变的腺瘤——通常会。其他HNPCC肿瘤也不一致地表现出MSI。

第二点涉及符合Amsterdam标准的家族，但没有检测到突变、负性MSI结果和未揭示IHC。这些家族可能会因为符合Amsterdam标准而认为可能表现出Lynch综合征。三个小组（包括我们小组，以及作者引用的一个小组）已证明这样的家族不会出现HNPCC中发现的超过额外的病变。甚至结肠癌的表型，在年龄、发病风险和亲属的风险上，比发现突变的Lynch综合征家族更轻。

第三，作者在评论中指出，导致30%的结肠癌的发病机制可能包括遗传变异。许多小组正在寻找这种背景下的易感基因——这些基因的渗透性较低，表型也不及Lynch综合征家族严重。

目前推荐的筛查策略为，家族中有多个结肠息肉患者和存在风险家族成员的家庭中的成员，应从20岁开始每1–2年进行一次结肠镜检查，检测并切除任何检测到的腺瘤样息肉。作者指出，这种策略的遵守度通常很低。
cancer or a case diagnosed under the age of 50 years, but no apparent Lynch syndrome, involves colonoscopy starting at age 40 (or at 10 years younger than the earliest case in the family), which should be repeated every 5 years. These recommendations would also seem reasonable for Amsterdam criteria-positive families who do not appear to have Lynch syndrome, except that there should be the option to repeat colonoscopy every 3 years. The shortened interval is suggested because of the known propensity of precancerous lesions to progress much faster in Lynch syndrome and because there remains some possibility of that diagnosis despite the negative genetic testing. After individuals in such a family have been screened for a number of years, the screening might either be relaxed or made more aggressive, depending on follow-up findings.

**Hamartomatous Polyposis Syndromes**
These syndromes, once thought to be benign syndromes of intestinal hamartomatous polyps, are now known to carry a rather extreme malignancy risk, both in the gastrointestinal tract and in extraintestinal areas [9]. It is questionable whether genetic testing would be helpful in Peutz-Jeghers syndrome, as the typical perioral pigmentation is almost universally present in those with this condition. Also, the polyps are histologically specific for the syndrome. Sporadic Peutz-Jeghers polyps are found but only rarely.

Juvenile polyposis syndrome is quite different. Although juvenile polyps are histologically characteristic, they are found in approximately 1% to 3% of children, sporadically in adults, and in several inherited syndromes. These syndromes include juvenile polyposis syndrome, Cowden syndrome, and Bannayan-Ruvalcaba-Riley syndrome. The first syndrome arises from mutations of SMAD4 and BMPR1A, as described in the review, while the second two arise from mutations of the PTEN gene. Thus, genetic testing is likely to be quite helpful in distinguishing these diseases.

**Conclusions**
The paper by Jeter and colleagues summarizes an important emerging area of medicine. Genetic testing is now available for each of the syndromes of inherited colon cancer, and screening strategies can effectively prevent cancer in affected patients and families. Thus, it is inherently important for physicians to recognize these syndromes, be familiar with the related cancer risks, appropriately apply genetic testing, and effectively institute established screening guidelines to prevent or detect the related cancers early in their course. To this end, the review represents an important source of information for physicians.

**Disclosures:**
The author(s) have no significant financial interest or other relationship with the manufacturers of any products or providers of any service mentioned in this article.

**References:**


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