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Colorectal polyposes: From phenotype to diagnosis

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Abstract

The colorectal polyposes are uncommon and frequently present diagnostic difficulties. Although the final diagnostic arbiter is the demonstration of a germline mutation, this may not always be demonstrable, and some forms of colorectal polyposis have no known genetic basis. Therefore, an accurate description of the phenotype by the pathologist is central to the establishment of a working diagnosis. This can direct the search for the underlying genetic cause (if any) and is also essential for establishing the magnitude of risk of colorectal malignancy for the patient and the patient's relatives. The pathologist may be provided with only a small and selected sample of endoscopically resected polyps or with prodigious numbers of polyps (too many to sample) when receiving a surgical specimen. Each type of polyposis presents its own particular diagnostic problems that may relate to polyp numbers, gross recognition of small or flat polyps, incomplete development of the full phenotype at the stage of investigation, and the histological classification of unusual or mixed polyps. The aim of this review is to highlight the principles and pitfalls in achieving a comprehensive description of the various types of colorectal polyposis, including classical FAP, attenuated FAP, *MUTYH*- (formerly *MYH*-) associated polyposis (MAP), other presentations of multiple adenomas, Peutz-Jeghers syndrome (P-JS), juvenile polyposis syndrome (JPS), Cowden syndrome (CS), hereditary mixed polyposis syndrome (HMPS), and hyperplastic polyposis syndrome (HPS).

Keywords: Colon; Polyposis; Familial; Genotype; Phenotype

Introduction

The colorectal polyposes present a diagnostic challenge for the pathologist. Individually, the syndromes are rare and may show overlapping phenotypes. The polyps may differ morphologically from their sporadic counterparts, and two or more different types of polyp may occur in the same patient or surgical specimen. Polyps may be available only as a small and selected sample when removed endoscopically or in prodigious numbers (too many to sample) when presenting in a surgical specimen. Although each polyposis syndrome may have its own pattern of inheritance and set of extra-colorectal manifestations, this valuable clinical information may not be provided to the pathologist. It is nevertheless important to achieve a working diagnosis that is based on all the available evidence. This can direct the search for the underlying genetic cause (if any) and is also essential for establishing the magnitude of risk of colorectal malignancy for the patient and the patient's relatives. An accurate description of the phenotype is also useful for achieving meaningful genotype:phenotype correlations.

This review will begin with a brief overview of classical familial adenonatous polyposis (FAP) but will thereafter focus on colorectal polyposes that may be

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diagnostically challenging: attenuated FAP (AFAP), *MUTYH*- (formerly *MYH*-) associated polyposis (MAP), other presentations of multiple adenomas, Peutz-Jeghers syndrome (P-JS), juvenile polyposis syndrome (JPS), Cowden syndrome (CS), hereditary mixed polyposis syndrome (HMPS), and hyperplastic polyposis syndrome (HPS). Many of these colorectal polyposes have been documented comparatively recently, and some, notably HMPS and HPS, remain poorly characterized. Examples will be shown of diagnostic errors that appear with surprising frequency in the literature. This highlights the importance of obtaining a precise description of phenotype. Each type of polyposis presents its own particular diagnostic problems that may relate to polyp numbers, gross recognition of small or flat polyps, incomplete development of the full phenotype at the stage of investigation, and the histological classification of polyps.

Familial adenomatous polyposis (FAP)

Despite its importance as a tumorigenic model, FAP accounts for $<1\%$ of colorectal cancers. This low figure reflects the rarity of the condition (occurs in approximately 1 in 8000 subjects) but is also due to cancer prevention in known affected subjects. The presence of extra-colorectal features (sebaceous cysts, bone tumors, and fibromatosis) was first noted by Gardner [24]. The list of extra-colorectal features has gradually extended to include peri-ampullary adenoma and carcinoma, medulloblastoma, papillary carcinoma of thyroid, hepatoblastoma, fundic gland polyps and carcinoma of the stomach, and congenital hypertrophy of retinal pigmented epithelium (CHRPE) [55]. The presence of >100 colorectal adenomas has traditionally been used to distinguish the autosomal dominant condition FAP from multiple adenomas [11]. It is essential to obtain a tissue diagnosis, even when innumerable colorectal polyps are discovered in the child of an affected parent. Children may develop an unrelated and self-limited lymphoid polyposis that is indistinguishable at endoscopy from FAP. Since the phenotype does not usually develop until the second decade, less than 100 adenomas may be present in some affected children who are endoscoped prematurely. Although the vast majority of colorectal polyps are typical adenomas, hyperplastic polyps and serrated adenomas may occasionally be diagnosed [60].

The initial identification of the causative gene occurred through the discovery of a large interstitial deletion in chromosome 5q in a subject with Gardner syndrome [30], confirmation of the 5q21 locus through linkage analysis [6], identification of the *APC* gene by positional cloning, and finally the demonstration of truncating mutations in *APC* in the germline of affected subjects [27]. The multifunctional APC protein is large and comprises several motifs and domains, allowing it to oligomerize and/or interact with multiple molecules that include β-catenin, α-catenin, GSK3β, axin, conductin, and tubulin [55]. Although the diagnosis of FAP may be confirmed by the demonstration of a germline *APC* mutation, truncating *APC* mutations are found in only 70–90% of individuals or families with the FAP phenotype. Truncating mutations have been found throughout the *APC* gene. Most truncating mutations are fully penetrant but may be associated with a differing severity of colorectal polyposis and differing risks of the extra-colorectal manifestations [72]. Mutations in the central region of *APC* (codons 1290–1400) are associated with the most severe polyposis phenotype (Fig. 1). Two codons (1061 and 1309) are mutational hotspots and account for 11% and 17% of all germline mutations, respectively. CHRPE is associated with mutations between codons 457 and 1444, while jaw osteomas and fibromatosis (desmoids tumors) are more prevalent in patients with mutations occurring after codon 1400 [55].

A phenotype fully consistent with FAP may present in subjects with no family history of the condition. This may be due to a new mutation (accounts for one in four of new diagnoses), non-paternity, adoption, or denial of a family history. The FAP phenotype may also occur in subjects without a germline *APC* mutation. An explanation other than simple technical failure is the recently recognized autosomal recessive condition known as *MUTYH*- (formerly *MYH*-) associated polyposis (MAP) (see below). A variant of FAP in which there is an autosomal dominant predisposition to multiple but fewer than 100 adenomas has been described as attenuated FAP.

Attenuated FAP

The concept of AFAP began with the documentation of a large 'multiple adenoma family' characterized by the presence of less than 100 adenomas per subject [52]. The adenomas were mainly proximally located, tended to be flat, and colorectal cancers were relatively late in onset. There was a lack of extra-colorectal features. This family was originally diagnosed as having Lynch syndrome or hereditary non-polyposis colorectal cancer (HNPCC), and this led to the concept of flat adenomas being characteristic of Lynch syndrome/HNPCC [49]. Because adenomas in Lynch syndrome are more likely to be proximally located [20] and proximal adenomas are more likely than distal adenomas to be flat [80], there is probably a weak connection between flat adenomas and both AFAP and Lynch syndrome [50]. However, it is likely that the more definitive connection is between flatness and anatomic (proximal) location [80]. Linkage