Polyposis Syndromes
Role of the Pathologist

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• Gastrointestinal • Polyposis • Cancer • Syndrome

ABSTRACT

This article reviews the major gastrointestinal polyposis syndromes, with an emphasis on the molecular, clinical, and histopathological features of each. Salient features helpful in making or suggesting the diagnosis of these syndromes are discussed, as is the use of ancillary techniques, such as immunohistochemistry and molecular diagnostic studies in diagnosis confirmation and family screening.

Abbreviations: Polyposis

APC	Adenomatous polyposis coli
CCS	Cronkhite-Canada syndrome
CHRPE	Congenital hypertrophy of the retinal pigment epithelium
CIMP	CpG island methylator phenotype
FAP	Familial adenomatous polyposis
GI	Gastrointestinal
HNPCC	"Hereditary non-polyposis colorectal cancer syndrome"
JPS	Juvenile polyposis syndrome
LS	Lynch syndrome
MLPA	Multiplex ligation-dependent probe amplification
MSI-H	High-level microsatellite instability
MutYH formerly *MYH*	"MutY homologue"
PHS	*PTEN*-hamartoma syndrome/ Cowden/Bannayan-Riley-Ruvalcaba
PJS	Peutz-Jeghers syndrome
SCTAT	Sex cord tumor with annular tubules

OVERVIEW

Gastrointestinal (GI) polyposis syndromes are a challenging group of diagnoses for both surgical pathologists and patients. The distribution of the polyps in these syndromes can vary throughout the GI tract, and different entities (or even different manifestations of the same syndrome) may have a handful of polyps or hundreds to thousands of polyps affecting 1 or more organs. In addition, some syndromes have extra-GI manifestations, many have polyps with overlapping histologic features, and not all are associated with an increased risk of GI cancer. Furthermore, important clinical and hereditary information that could provide a clue to diagnosis may not accompany biopsies sent to a surgical pathologist. Thus, a high index of suspicion for a microscopic appearance and any clinical clues to the possibility of a polyposis syndrome must be maintained to make (or even suggest) an accurate diagnosis.

Recent advances in molecular diagnostic techniques and in understanding the genetic basis of these syndromes provide an opportunity for ancillary studies that aid both patient care teams and, potentially, the families of affected patients. An understanding of the molecular genetic pathology underlying such syndromes can aid pathologists in seeking the appropriate histologic features to suggest the diagnosis and in providing advice to clinical colleagues for further studies and family counseling, an opportunity to provide personalized

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medicine. This review addresses the clinical, histologic, and molecular aspects of the major GI polyposis syndromes, with an emphasis on the role of surgical pathologists in tissue diagnosis and in understanding and guiding the appropriate use of ancillary modalities, such as molecular diagnostic pathology.

FAMILIAL ADENOMATOUS POLYPOSIS

Inherited in an autosomal dominant and highly penetrant fashion, familial adenomatous polyposis (FAP) usually results from an inherited germline mutation in the *adenomatous polyposis coli (APC)* gene on chromosome 5 (5q21-q22).[1–4] *APC* is a tumor suppressor gene that functions in the *Wnt* signaling pathway by down-regulating β-catenin, and loss of its function allows the accumulation of mutations in additional, important genetic loci, such as *TP53*, *RAS*, and others.[1,5] Although FAP is the most common genetic polyposis syndrome, its incidence is much less than 1% of the population.

CLINICAL AND GROSS FEATURES

Most patients with the classic syndrome present by age 20 with hundreds or thousands of adenomatous colonic polyps (more than 100 polyps, by definition) that carpet the mucosa (**Fig. 1**), although there is an attenuated version in which patients tend to present later and have fewer polyps (fewer than 100 by definition but most often fewer than 30) that tend to concentrate in the right colon. The attenuated phenotype results from mutations at either end of the *APC* gene.[2,5] In addition to its manifestations in the colon, FAP has other characteristic features. First, adenomas can occur elsewhere in the GI tract, especially the duodenum. In the stomach, true adenomas can occur, as can fundic gland polyps, with or without epithelial dysplasia (**Fig. 2**). Extra-GI manifestations include osteomas of the mandible, desmoid fibromatosis (**Fig. 3**), and other soft tissue tumors, including leiomyomas and lipomas, as well as CHRPE. The constellation of adenomatous polyposis with prominent extracolonic manifestations, such as these (especially desmoid fibromatosis) is termed, *Gardner syndrome*. In addition, some FAP patients may have brain tumors (especially medulloblastomas in children), a combination termed, *Turcot syndrome*. A variety of other tumors have been associated with FAP, including hepatocellular carcinoma, hepatoblastoma, papillary thyroid carcinoma, adrenal cortical neoplasms, and nasopharyngeal angiofibromas.[2,6]

MICROSCOPIC FEATURES

The adenomas and tumors occurring in the setting of FAP are histologically indistinguishable from their sporadic counterparts, with crowded, pseudostratified, elongated, and hyperchromatic epithelial nuclei (**Fig. 4**). The histologic hallmark of FAP patients is the so-called unicryptal adenoma (**Fig. 5**), which can be seen on routine biopsy sections but is most easily identified by submission of en face mucosal (Bussey) sections (**Fig. 6**).[5]

Fig. 1. Colectomy specimen from patient with FAP, with innumerable polyps of variable size and morphology carpeting the mucosal surface.