Table 17-10 Gastrointestinal Polyposis Syndromes

Syndrome	Mean Age at Presentation (yr)	Mutated Gene(s); Pathway	Gastrointestinal Lesions	Selected Extra-Gastrointestinal Manifestations
Juvenile polyposis	<5	*SMAD4,BMPR1A*; TGF-β signaling pathway	Juvenile polyps; risk of gastric, small intestinal, colonic, and pancreatic adenocarcinoma	Congenital malformations, digital clubbing
Peutz-Jeghers syndrome	10-15	*STK11*; AMP kinase-related pathways	Arborizing polyps; Small intestine > colon > stomach; colonic adenocarcinoma	Pigmented macules; risk of colon, breast, lung, pancreatic, and thyroid cancer
Cowden syndrome, Bannayan-Ruvalcaba-Riley syndrome*	<15	*PTEN*: PI3K/AKT pathway	Hamartomatous/ inflammatory intestinal polyps, lipomas, ganglioneuromas	Benign skin tumors, benign and malignant thyroid and breast lesions; no increase in GI cancers
Cronkhite-Canada syndrome	>50	Nonhereditary, unknown cause	Hamartomatous polyps of stomach, small intestine colon; abnormalities in nonpolypoid mucosa	Nail atrophy, hair loss, abnormal skin pigmentation, cachexia, and anemia. Fatal in up to 50%.
Tuberous sclerosis		*TSC1* (hamartin), *TSC2* (tuberin); mTOR pathway	Hamartomatous polyps	Mental retardation, epilepsy. facial angiofibroma, cortical (CNS) tubers, renal angiomyolipoma
Familial adenomatous polyposis (FAP)				
Classic FAP	10-15	*APC*	Multiple adenomas	Congenital RPE hypertrophy
Attenuated FAP	40-50	*APC*	Multiple adenomas	
Gardner syndrome	10-15	*APC*	Multiple adenomas	Osteomas, thyroid and desmoid tumors, skin cysts
Turcot syndrome	10-15	*APC*	Multiple adenomas	Medulloblastoma, glioblastoma
MYH-associated polyposis	30-50	*MYH*	Multiple adenomas	

CNS, Central nervous system; mTOR, mammalian target of rapamycin; RPE, retinal pigmented epithelium.
*Also called PTEN Hamartoma-Tumor Syndromes.

MORPHOLOGY

Most juvenile polyps are less than 3 cm in diameter. They are typically pedunculated, smooth-surfaced, reddish lesions with characteristic cystic spaces apparent after sectioning. Microscopic examination shows these cysts to be dilated glands filled with mucin and inflammatory debris (Fig. 17-43). The remainder of the polyp is composed of lamina propria expanded by mixed inflammatory infiltrates. The muscularis mucosae may be normal or attenuated.

Although the morphogenesis of juvenile polyps is incompletely understood, it has been proposed that mucosal hyperplasia is the initiating event. This hypothesis is consistent with the discovery that mutations in pathways that regulate cellular growth cause autosomal dominant juvenile polyposis. The most common mutation identified is of *SMAD4*, which encodes a cytoplasmic intermediate in the TGF-β signaling pathway. *BMPR1A*, a kinase that is a member of the TGF-β superfamily, may be mutated in other cases (Table 17-10). However, these mutations account for fewer than half of patients, suggesting that other genes responsible for autosomal dominant juvenile polyposis remain to be discovered.

Dysplasia is extremely rare in sporadic juvenile polyps. In contrast juvenile polyposis syndrome is associated with dysplasia, both within the juvenile polyps and in separate adenomas. As a result, 30% to 50% of patients with juvenile polyposis develop colonic adenocarcinoma by age 45.

Peutz-Jeghers Syndrome

This rare autosomal dominant syndrome presents at a median age of 11 years with multiple GI hamartomatous polyps and mucocutaneous hyperpigmentation. The latter takes the form of dark blue to brown macules on the lips, nostrils, buccal mucosa, palmar surfaces of the hands, genitalia, and perianal region. These lesions are similar to freckles but are distinguished by their presence in the buccal mucosa. Peutz-Jeghers polyps can initiate intussusception, which is occasionally fatal. Of greater importance, *Peutz-Jeghers syndrome is associated with a markedly increased risk of several malignancies*. Lifetime risk is approximately 40% for these, and regular surveillance is recommended beginning at birth, for sex cord tumors of the testes; late childhood for gastric and small intestinal cancers; and the second and third decades of life for colon, pancreatic, breast, lung, ovarian, and uterine cancers.

Pathogenesis. Germline heterozygous loss-of-function mutations in the gene *STK11* are present in approximately half of individuals with familial Peutz-Jeghers syndrome as well as a subset of patients with sporadic Peutz-Jeghers syndrome. You will recall from Chapter 7 that *STK11* is a tumor suppressor gene that encodes a kinase that regulates cell polarization and acts as a brake on growth and anabolic metabolism. As is common with other tumor suppressor genes, the function of the second "normal" copy of *STK11* is often lost through somatic mutation in cancers occurring in Peutz-Jeghers syndrome, providing an explanation for the high risk of neoplasia in affected patients. Importantly, colon cancers can also develop at sites without Peutz-Jeghers polyps.

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