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Phenotype and Cancer Risk of Various Polyposis Syndromes

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The gastrointestinal polyposis syndromes are disorders with multiple intestinal polyps. Three of these disorders, familial adenomatous polyposis, Peutz–Jeghers syndrome and juvenile polyposis are associated with increased risk of colorectal as well as extracolonic cancers. A description of the phenotype and associated cancer risk is provided for each.

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INTRODUCTION

THE GASTROINTESTINAL polyposis syndromes are disorders with multiple intestinal polyps. Familial adenomatous polyposis (FAP), Peutz–Jeghers syndrome and juvenile polyposis are illnesses associated with both colorectal and extracolonic neoplasia. They are best categorised and differentiated by polyp histopathology. This review will describe the phenotypic characteristics and the association with colorectal neoplasia of these syndromes.

FAMILIAL ADENOMATOUS POLYPOSIS

Phenotypic characteristics

FAP is an autosomal dominant syndrome caused by a germline mutation of the *APC* (adenomatous polyposis coli) gene located on chromosome 5q (1, 2]. This disorder affects both sexes equally and is seen worldwide.

Patients with FAP develop hundreds to thousands of colorectal adenomas, usually in adolescence. Data from Petersen and associates revealed that 50% of FAP patients develop adenomas by 15 years of age and 95% by age 35 years (G.M. Petersen, personal communication). Polyps occur diffusely throughout the colorectum. However, the density and size of adenomas can vary throughout the large intestine, even in patients with identical germline mutations of the *APC* gene [3]. The histopathology of adenomas can be tubular, tubulovillus, villus or frank adenocarcinoma within adenomas.

Colorectal cancer

Inevitably, FAP patients develop colorectal cancer usually by the fifth decade of life if colectomy is not performed [4, 5]. Colorectal cancer occurs primarily in the left colon (84%); the average age at diagnosis of colorectal adenocarcinoma ranges between 34.5 and 43 years [4, 6]. Recently, Caspari and associates have reported that mutation at codon 1309 of the *APC* gene is associated with early onset of colon cancer compared to patients with other *APC* gene mutations [7]. Death from colorectal cancer in untreated patients occurs on average at 42 years of age.

Benign extracolonic manifestations

Patients can acquire a variety of benign extracolonic manifestations [4]. Extracolonic polyps include adenomas of the small intestine found primarily in the duodenum clustered around the papilla of Vater. Adenomas and fundic gland retention polyps are found in the stomach. Cutaneous lesions also occur, and include epidermoid cysts, fibromas, lipomas and sebaceous cysts [8].

Desmoid tumours are fibromatous lesions occurring in the extremities, abdominal wall and the mesentery of approximately 10% of FAP patients [9]. Desmoids, particularly of the mesentery, can grow locally causing a host of complications.

Osteomas are benign lesions which develop in the skull, long bones and characteristically in the mandible at the angle of the jaw. These lesions, readily appreciated by physical examination, are usually asymptomatic, but occasionally grow causing local problems. Occult radio-opaque jaw lesions (ORJL) are osteosclerotic, asymptomatic lesions seen on panoramic jaw radiographs.

Pigmented ocular fundus lesions (POFLs), also called congenital hypertrophy of the retinal pigment epithelium (CHRPE), are discrete, round to oval, darkly pigmented areas from 0.1 to 1.0 optic-disc diameters in size detected on the retina by indirect ophthalmoscopy. An association between the occurrence of POFLs and the location of germline *APC* gene mutation has been reported [10]. Importantly, the presence of ORJLs or POFLs in an at risk individual is predictive of FAP [11]. Nasopharyngeal angiofibroma is a highly vascular, locally invasive tumour, occurring almost exclusively in the nares or nasopharynx of male adolescents [12].

Malignant extracolonic manifestations

Patients with FAP are at risk for several extracolonic malignancies. The lifetime risk of a FAP patient developing these malignancies is seen in Table 1.

Hepatoblastoma is a rare, malignant, rapidly fatal, embryonal liver cancer occurring in the first 5 years of life in approximately 1.6% of the offspring of FAP parents [13]. This rapidly progressive tumour is potentially curable by removal, but carries a

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Table 1. *Extracolonic cancer*

Malignancy	Relative risk	Absolute lifetime risk (%)
Brain	7.0	2.0
Thyroid	7.6	2.0
Duodenum	330.8	3.0
Ampullary	123.7	1.7
Pancreas	4.5	1.7
Hepatoblastoma	847.0	1.6

Note: The rate of stomach and non-duodenal small intestinal cancer is not statistically different from the general population.

grave prognosis when malignancy has spread beyond surgical resection.

Upper gastrointestinal tract malignancy including adenocarcinoma of the duodenum and periampullary region are second only to the colorectum as a site of malignancy in FAP patients [14]. A high percentage of gastric cancer has also been reported in some polyposis registries worldwide (in particular the Japanese) [14]. In fact, in Japan, gastric cancer is the second most common neoplasia after colorectal carcinoma in FAP patients. This seems to point to an environmental factor, given the already high risk of gastric cancer in the general Japanese population. However, an analysis of American FAP patients revealed a strikingly high relative risk of duodenal and ampullary adenocarcinoma, but no increased risk of gastric or non-duodenal small intestinal cancer compared with the general population [15].

Other extracolonic cancers noted in FAP patients are malignancy of the thyroid gland, biliary tree, pancreas and brain [16]. The relative risks of thyroid and pancreatic cancer are almost eight and five times that of the general population, respectively.

Patients with polyposis and brain tumour have been termed as having Turcot syndrome. The appellation "Turcot syndrome" appears to be used to delineate two genotypically different disorders [17]: (i) It can be considered simply as FAP in which the extracolonic lesion is a brain tumour. These patients have germline mutation of the *APC* gene. Brain neoplasms noted in adenomatous polyposis patients included primarily medulloblastomas. These tumours usually present in the second decade of life. (ii) Turcot syndrome has also been applied to families with brain tumours and a colorectal phenotype with as few as 5–10 adenomas (this was the original description by Turcot) [18]. This type of kindred is linked to mutation of DNA mismatch repair genes. Brain tumours also tend to be glioblastomas and astrocytomas [18a].

PEUTZ–JEGHERS SYNDROME

Phenotypic characteristics

Peutz–Jeghers syndrome is an autosomal dominant condition in which Peutz–Jeghers polyps occur primarily in the small intestine, but can also be found in the colon and stomach [19, 20]. The polyps usually number between one to 20 per intestinal segment. The Peutz–Jeghers polyp is a true hamartoma with unique histopathology, characterised by polyp epithelium supported by an arbourising framework of smooth muscle. The characteristic finding on physical examination is brown, macular, melanin pigmentation measuring 1–5 mm on the lips and buccal mucosa, sometimes on the digits of the hands and feet, and eyelids. The melanin spots appear in early childhood and can fade in late adolescence.

The primary complication of Peutz–Jeghers syndrome in childhood is small intestine intersusseption caused by small bowel polyps; intestinal bleeding can also occur. The genetic defect responsible for Peutz–Jeghers syndrome has not yet been identified.

Cancer risk

Peutz–Jeghers patients are at increased risk for both gastrointestinal and non-gastrointestinal cancer. We estimated that these patients have an 18-fold higher risk of adenocarcinoma than the general population [21]. Although neoplastic transformation of the Peutz–Jeghers polyp occurs infrequently, adults are at risk at a relatively young age for gastrointestinal adenocarcinoma, most commonly of the duodenum and stomach, but also including the pancreas. In addition, non-gastrointestinal cancers (i.e. breast, ovary, endometrium, testes) are seen in greater frequency and at a young age [21, 22]. Subsets of patients have both intestinal adenomas and hamartomas. Unusual tumours found are Sertoli cell tumour of the ovary and adenoma malignum of the cervix in women, and testicular cancer in prepubescent boys.

JUVENILE POLYPOSIS SYNDROMES

Phenotypic characteristics

Juvenile polyps are hamartomatous lesions with a distinct histopathology, characterised by oedematous mucosa and dilated mucus-filled cysts. The vast majority of individuals with juvenile polyps present in infancy or early childhood (average age of presentation 4 years old) with solitary juvenile polyps (one or two polyps) in the rectosigmoid colon. The usual symptoms are rectal bleeding or anal prolapse of a polyp. This appears to be a non-inherited condition.

In juvenile polyposis (patients with three or more juvenile polyps), three to hundreds of polyps occur primarily in the colorectum, but occasionally in the small intestine and stomach [23, 24]. In 30% of these cases, familial clustering with an autosomal dominant inheritance pattern is noted. Patients can present in late childhood or early adolescence (but can be preschoolers) with anaemia, rectal bleeding, failure to thrive, hypoalbunaemia and/or abdominal pain. Other individuals, with less polyp burden, can be asymptomatic. In non-familial cases of juvenile polyposis, congenital abnormalities have been reported.

Cancer risk

Patients with solitary juvenile polyps appear to be at no increased risk of colorectal cancer. When compared to the general British population, solitary juvenile polyp patients lived longer and had a comparable risk of colorectal cancer [25].

However, juvenile polyposis patients have a high incidence of colorectal neoplasia (dysplasia and adenocarcinoma). Colorectal neoplasia was found in up to 20% of patients at a relatively young age (average 37 years, but dysplasia has been found in the colectomy specimens of children less than 5 years of age) [26]. Colorectal neoplasia can be found in the juvenile polyps as well as the flat mucosa. Gastric, duodenal and pancreatic cancers also have been reported.

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