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Pathology and genetics of hereditary colorectal cancer

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Summary

Colorectal cancer (CRC) accounts for over 8% of all deaths annually worldwide. Between 2 and 5% of all CRCs occur due to inherited syndromes, including Lynch syndrome, familial adenomatous polyposis, MUTYH-associated polyposis, Peutz–Jeghers syndrome, juvenile polyposis and Cowden/PTEN hamartoma syndrome. In addition, serrated polyposis is a clinically defined condition characterised by multiple colorectal serrated polyps and an increased risk of CRC but the genetics are not known. In most hereditary CRC syndromes, polyps undergo carcinogenesis, but the exact route to carcinoma seems to differ between the conditions. Discovery of the key germline mutations in these syndromes has been instrumental to our understanding of the underlying molecular mechanisms of colorectal carcinogenesis. This review summarises the genetic and pathological alterations in hereditary CRC syndromes.

Key words: Familial colon cancer; hereditary polyposis syndrome; genetic defect.

Abbreviations: AFAP; attenuated familial adenomatous polyposis; CS; Cowden syndrome; FAP; familial adenomatous polyposis; JPS; juvenile polyposis syndrome; LS; Lynch syndrome; MAP; MUTYH-associated polyposis; PJS; Peutz–Jeghers syndrome; SPS; serrated polyposis syndrome.

INTRODUCTION

Colorectal cancer (CRC) accounts for over 8% of all deaths annually worldwide.[1] Both men and woman have an approximately 4.3% lifetime risk of CRC.[2] Although the exact causes of the vast majority of CRCs remain unknown, there are several risk factors, including age, personal and family history of CRC and diet.[3] Furthermore, 2–5% of all CRCs occur within inherited syndromes.[4]

Colorectal cancer syndromes are commonly subclassified as Lynch syndrome (previously known as hereditary non-polyposis colorectal cancer syndrome; HNPCC) or as one of the polyposis syndromes, characterised by the presence of multiple colorectal polyps. The gastrointestinal polyposis syndromes are further subclassified according to the predominant type of polyps, i.e., adenomatous polyps, hamartomatous polyps (juvenile or Peutz–Jeghers polyps) or serrated polyps. Some of the characteristic morphological features of these syndromes are shown in Fig. 1. Although the route to CRC formation differs among these syndromes, most are defined by single germline mutation in genes that play a role in genetic instability, cell proliferation, or potentially the regulation of the crypt niche microenvironment. Each of them results in a unique genetic disorder with accompanying clinical features and cancer risks (Table 1). In this review, we summarise the current knowledge about genetic and pathological alterations in these patients which eventually lead to CRC formation.

LYNCH SYNDROME (LS)

The most common hereditary CRC predisposing syndrome, Lynch syndrome (also known as hereditary non-polyposis colorectal cancer; HNPCC), is implicated in 2–4% of CRC cases.[5] LS is characterised by a high penetrance, early-onset colorectal cancer, and an increased risk of extra-intestinal cancers. Cancer risks vary between different germline mismatch repair gene mutations (Table 2).[6–8] LS patients develop CRC at an average age of 45 compared to 67 years in the general population. The characteristic pathology features of CRCs in Lynch syndrome include poorly differentiated carcinomas, mucinous carcinomas (Fig. 1B), and those exhibiting a Crohn's-like peri-tumoural inflammatory reaction and tumour-infiltrating lymphocytes.[9] The diagnosis of Lynch syndrome is based on the Amsterdam II criteria,[10] and the revised Bethesda criteria.[11]

LS is inherited in an autosomal dominant fashion, developing from a mutation in one allele of one of the DNA mismatch repair (MMR) genes, most commonly *MLH1* and *MSH2* (up to 90%), or less frequently *MSH6* (approximately 10%) and *PMS2* (rare occasions) (Fig. 2A–E).[9,12] In addition, a germline deletion in the epithelial cell adhesion molecule gene *EpCAM*, located upstream of *MSH2*, is an alternative cause of *MSH2* silencing causing LS.[13] Loss of functional MMR proteins leads to defects in DNA repair and, subsequently, high DNA microsatellite instability (MSI-High) (Fig. 2F). Loss of MMR proteins can be demonstrated by immunohistochemistry and used to identify tumours with MSI. In addition, MMR immunohistochemistry is a complementary diagnostic approach to screen for LS and pinpoint which gene is most likely mutated (Fig. 2E).[14] Approximately 15% of sporadic CRCs are also microsatellite instable, which results from hypermethylation of the promoter of *MLH1* (CpG island methylator phenotype; CIMP). This mechanism also results in loss of MLH1 protein expression by immunolabelling.[15] As

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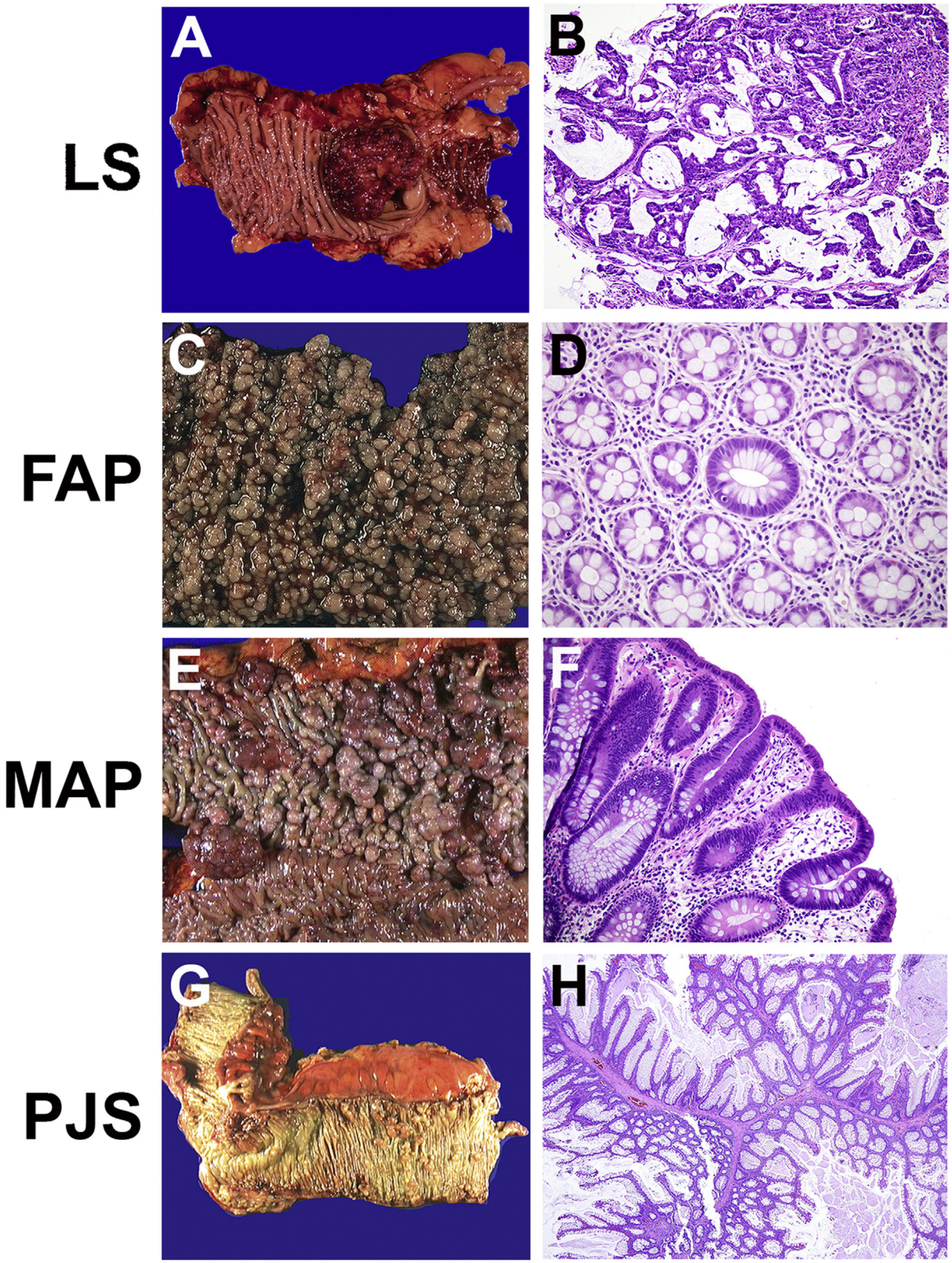

Fig. 1 Macroscopic and microscopic characteristics of each of the hereditary CRC syndromes. (A) Lynch syndrome (LS): this resection specimen shows a malignant tumour in the caecum and an otherwise unremarkable surrounding mucosa without polyps. (B) Histologically adenocarcinomas in LS are often characterised by mucinous (depicted in B) or poor differentiation and may exhibit a Crohn's-like peri-tumoural inflammatory reaction and tumour-infiltrating lymphocytes. (C) Familial adenomatous polyposis (FAP): macroscopically, classic FAP is characterised by innumerable mainly small adenomatous polyps carpeting the entire colonic mucosa. (D) Microscopically, adenomas in FAP are identical to their sporadic counterparts. In attenuated FAP there are fewer polyps and areas with macroscopically normal mucosa. However, the macroscopically normal appearing mucosa can harbour microscopic dysplastic crypts or aberrant crypt foci (ACF) that are characteristic for FAP. (E) MUTYH-associated polyposis (MAP): macroscopically MAP is characterised by the development of 10–100 adenomas in the colorectum, and resembles attenuated FAP. (F) The vast majority of polyps in MAP are conventional adenomas. (G) Peutz–Jeghers syndrome (PJS): the number of gastrointestinal polyps in PJS is much lower than in FAP and typically around a dozen. Colorectal PJS polyps vary in size from millimetres to several centimetres and are usually pedunculated with a smooth and lobulated surface. Histologically, the hamartomas show a tree-like configuration with arborising strands of smooth muscle and dilated crypts. (H) The polyps are lined by normal epithelium characteristic for the specific location.

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