

Familial adenomatous polyposis in China (Review)

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Abstract. Familial adenomatous polyposis (FAP) is an autosomal dominant disease with a poor prognosis, and has been studied by clinicians and geneticists in China for the past three decades. It is estimated that FAP has an incidence of between 1 in 8,000 and 1 in 10,000 individuals, and accounts for 0.94% of colorectal cancer cases in China. Recent advances in the understanding of FAP suggest that the genotype of the patient may allow for early diagnosis and surveillance, and guide surgical and chemopreventive management. However, the genetic mechanisms of FAP vary between different countries. FAP in China has its own characteristics, and this may be due to ethnic and geographical genetic variation. In the present review the clinical manifestations and genetics of FAP in China are discussed, as well as the surgical strategies, chemotherapeutics and traditional Chinese medicines used in its treatment. Increased insight into the genetic and clinical features of FAP in the Chinese population may aid in the prevention and management of the disorder.

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1. Introduction

Familial adenomatous polyposis (FAP) is an inherited disorder characterized by the development of hundreds to thousands of adenomas in the rectum and colon during the second decade of life (1-3). According to previous reports, including the Chinese cancer registry annual report (4), FAP in China has an incidence at birth of between 1 in 8,000 and 1 in 10,000 individuals; it manifests equally in males and females, and accounts for 0.94% of colorectal cancer (CRC) cases. Prevalence of FAP in China has been estimated to be 1-1.5 in every 100,000 individuals (5-8).

Researchers in China have studied FAP for >30 years (5-10). Clinically, patients with FAP presenting with numerous colorectal adenomas are easy to diagnose (11); however, it is desirable to screen out high-risk patients at earlier stages of development. Currently, only certain individuals presenting with typical extra-colonic manifestations, including congenital hypertrophy of the retinal pigment epithelium (CHRPE), are recognized as high-risk (7,8,11,12). In 1991, Groden *et al* (13) observed that FAP is caused by germline mutations in the adenomatous polyposis coli (APC) gene, and subsequent research confirmed that FAP is an autosomal dominant disease (14-17). Members of families with a frequent history of FAP may be at high risk of developing the disease (15).

FAP is divided into three subtypes, including classic FAP (CFAP), attenuated FAP (AFAP) and mutY DNA glycosylase (MUTYH)-associated polyposis (MAP), each with unique genetics, clinical features and prognoses (15,16). Germline mutations and large rearrangements in the APC gene are the primary causes of CFAP and AFAP (16-19), while mutations in the MUTYH gene cause MAP (20-23). Increasing numbers of pathogenic mutations have been reported to predispose patients to FAP, and recent advances in the understanding of FAP suggest that the genetics of each patient may allow for early diagnosis and surveillance, and guide surgical and chemopreventive management (24,25). However, the genetics of FAP vary markedly between countries (26-33). FAP in China has its own unique characteristics, with the genotypes of patients with FAP varying between regions and ethnicities (5,34-36).

As in Western countries, the primary priority for patients with FAP in China is maintenance of a high quality of life (5). In the present review, the clinical manifestations and genetics of FAP in China are discussed, as well as the surgical strategies, chemotherapeutics and traditional Chinese medicines (TCM)

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used in its treatment. Increased insight into the genetic and clinical features of FAP in the Chinese population may aid in the prevention and management of the disorder.

2. Data collection

PubMed (www.ncbi.nlm.nih.gov/sites/entrez?db=PubMed) and Chinese search engines, including CNKI Data (www.cnki.net), Wanfang Data (www.wanfangdata.com.cn), SinoMed (www.sinomed.imicams.ac.cn) and Vip Information (www.cqvip.com), were used to search the literature for reference to FAP in China, using the key words: 'familial adenomatous polyposis', 'APC', 'MYH' and 'Chinese'.

The majority of data on the genetic variations of FAP in China is derived from published articles, databases and unpublished experimental research, including the UMD APC mutations database (www.umd.be/APC), APC-Database (www.LOVD.nl/APC), Zhejiang University-Adinovo Center APC Database (www.genomed.org/lovd2/home.php?select_db=APC) (37) and the APC Mutation Database (fap.taenzer.me). The MUTYH Mutation Database (www.LOVD.nl/MUTYH) was used to search for variation in the MUTYH gene.

3. Clinical manifestations

Colonic manifestations. It is established that there are primarily three subtypes of FAP. CFAP is the most common clinical phenotype and is characterized by the presence of numerous colorectal adenomas of differing sizes (Fig. 1), which if left untreated progress into CRC. The majority of FAP cases in China belong to this subtype (34-37). AFAP is a less severe form of FAP, characterized by the presence of <100 polyps and a later onset of CRC. AFAP in China has only been diagnosed as an independent subclass to CFAP in the past ten years (38-40). MAP is characterized by multiple adenomatous polyps, with the majority of patients with MAP presenting with fewer polyps compared with patients with CFAP. MAP is reported to be the least common subtype, accounting for 1-5% of FAP cases in China. This apparent decreased prevalence in MAP may be due to poor recognition and detection of MAP (41-44).

Extra-colonic manifestations. Individuals with FAP are reported to develop a variety of extra-colonic gastrointestinal manifestations (45,46). However, fundic gland polyps in the stomach, adenomatous polyps in the duodenum and periampullary region, and cancerization of upper gastrointestinal adenomas is rare in Chinese patients with FAP, particularly in those with CFAP (47). In 2015, Yan *et al* (48) reported a case of acute cholangitis due to adenomas of the CBD in a patient with FAP, accompanied by adenomatous changes in the stomach, duodenum and the ampulla of Vater.

Extra-intestinal manifestations of FAP consist mainly of cutaneous lesions, including fibromas, lipomas, and sebaceous and epidermoid cysts (49,50). There are specific FAP-associated syndromes reported in China, including Gardner syndrome and Turcot syndrome (51). CHRPE is another characteristic extra-intestinal manifestation in patients with FAP (52). In 1995, Li *et al* (53) initially reported CHRPE in 6 patients with CFAP, and in 2010, Ding *et al* (54) detected CHRPE in

22 patients with FAP, suggesting that CHRPE is an indicator of patients at a high risk of FAP.

4. Role of mutations

Mutation analysis of the APC gene. The Leiden Open Variation Database reported >1600 different pathogenic APC mutations (www.chromium.lovd.nl/LOVD2/colon_cancer/home.php?select_db=APC). A total of 275 of these mutations were reported in China, 194 of which are unique to China (37). The majority of mutations are nonsense mutations or small insertions and deletions, which lead to a truncated APC protein. Mutations causing FAP in China have been reported to occur mainly in three regions of the APC gene: At the 5' end, prior to codon 500; near codon 1309 in the largest exon 16; or at the 3' end, following codon 1580 (37).

The mutation cluster region (MCR) in the APC gene in Western countries has been established to be localized between codons 1250 and 1464 (55,56). However, among the Chinese population, the MCR in the APC gene is not consistent with Western countries, instead localizing to exon 16, between codon 849 and 1376 (Fig. 1). According to the Chinese APC database: The 5 bp deletion, c.3927_3931delAAAGA, at codon 1309 was reported on eight occasions; the nonsense substitution, c.3925G>T, at codon 1309 was reported on two occasions; the 2 bp deletion, c.3182_3183delAA was reported once; the 5 bp deletion, c.3181_3185delAAACA, at codon 1061 was reported once; and the 5 bp deletion, c.3183_3187delACAAA, at codon 1061 was reported on three occasions (37). The aforementioned data indicate that the APC gene is frequently mutated between codons 1309 and 1061 in Chinese families with FAP, which is consistent with Western families (57). Furthermore, the substitution, c.4479G>A, at codon 1493 was reported on five occasions; the 2 bp deletion, c.4393_4394delAG, at codon 1465 was reported on four occasions; the nonsense substitution, c.4012C>T, at codon 1338 was reported on four occasions; and the nonsense substitution, c.994C>T, at codon 332 was reported on four occasions. The data suggest that the APC gene may frequently contain polymorphisms at these points in Chinese patients with FAP (37).

Certain rare mutations of the APC gene have been reported in Chinese patients with FAP, including intron or promoter point mutations. For example, the following mutations have been detected in Chinese patients with FAP (58,59): The nonsense substitution, c.220+40T>C, at intron 2+39; the nonsense substitution, c.645+32C>T, at intron 5+32; the 1 bp deletion, c.645+46delG, at intron 5+46. Furthermore, the nonsense substitutions, c.1556C>G and c.1753G>A, have been reported at the 3' untranslated region of the APC gene. However, the pathogenicity of these mutations remains unclear.

MUTYH mutation screening. There is no specialized website or database devoted to mutations in the MUTYH gene in China, as the majority of MUTYH gene screening is conducted sporadically in patients with CRC and few of these screenings were performed in Chinese patients with MAP. In 2008, Tong *et al* (43) identified three single nucleotide polymorphisms (SNPs) of the MUTYH gene, including IVS1-5A>C, IVS6+35A>G and c.G972C (Q335H). The SNP IVS1-5A>C was confirmed to be significant in the etiopathogenesis of

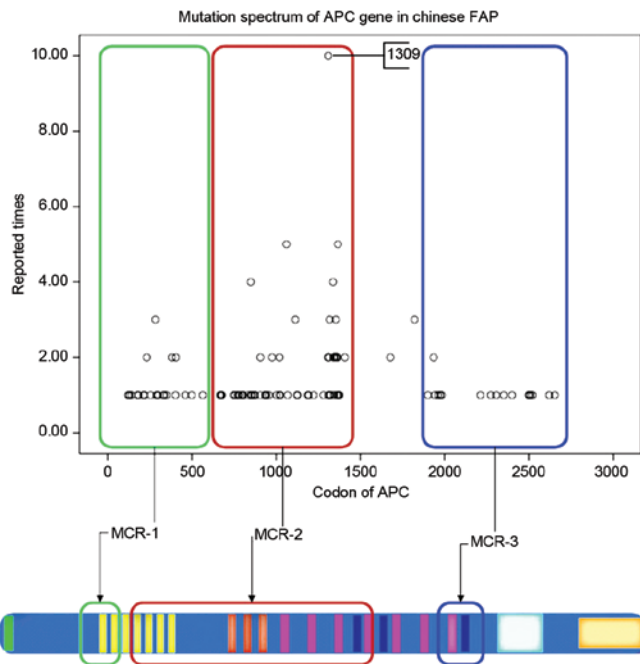


Figure 1. Mutation spectrum of the APC gene in FAP in the Chinese population. MCR-1, APC mutation variants identified at the 5' end (before codon 500). MCR-2, APC mutation variants identified between codon 849 and 1376. MCR-3, APC mutation variants identified at the 3' end (after codon 1580). APC, adenomatous polyposis coli; FAP, familial adenomatous polyposis; MCR, mutation cluster region.

CRC, and may be used in screening of high-risk patients (43). Currently, p.Y165C and p.G382D mutations in the MUTYH protein have only been observed in patients from Western countries (60,61) and there is no identified polymorphism in the MUTYH gene for MAP patients in China.

Conventional screening techniques fail to identify ~30% of families with CFAP and ~90% of families with AFAP. A large subset of families with history of FAP have undetectable pathogenic changes defined as APC(-) and MUTYH(-) FAP (62,63). No other specific genes predisposing an individual to FAP have been identified in China (41).

5. Surgical strategies

Surgical intervention is the most effective therapy for patients with FAP who present with colonic disorders, and prophylactic removal of the tumorigenic colon is considered to be the standard treatment for FAP (64,65). The surgical strategies and optimal time of intervention vary between each FAP subtype (64-66). In China, patients with CFAP and advanced AFAP may be treated by total proctocolectomy with ileostomy, subtotal colectomy with ileorectal anastomosis (IRA), total colectomy or proctocolectomy with ileo-anal pouch anastomosis (IPAA), total colectomy or proctocolectomy with IPAA, subtotal colectomy plus rectal mucosectomy, IPAA through the muscular sheath of the rectum, IPAA alone and subtotal proctocolectomy (66,67). IPAA offers the best available prophylaxis in CFAP patients and remains the primary alternative to IRA (66). Furthermore, laparoscopic IPAA surgery is performed in Chinese patients with FAP, and is considered to be safe, feasible and effective (68).

Patients with early stage AFAP and MAP have increased available treatment options compared with patients with CFAP and advanced AFAP (69,70). Due to rapid progress in colonoscopy, doctors in China are able to remove numerous adenomas using endoscopic polyp electrocision and endoanal mucosal stripping (69). In 2006, He *et al* (71) reported the excision of 256 polyps in a single patient with FAP.

6. Chemoprevention

In order to delay the development of adenomas into adenocarcinoma and to prevent the recurrence of adenomas in the retained rectum of patients with FAP following surgical intervention, multiple drugs and dietary supplements have been identified as potential chemopreventatives (72,73). The nonsteroidal anti-inflammatory drug (NSAID) sulindac (74,75) and selective cyclooxygenase-2 (COX-2) inhibitor celecoxib (76,77) are the typical drugs administered to control and reduce polyposis in the retained rectum following surgery. However, gastrointestinal toxicity has been observed following long-term treatment with non-selective NSAIDs (78), leading to an increase in the use of COX-2 inhibitors as the primary chemopreventive agent for patients with FAP (79,80). Treatment with celecoxib alone or combined with endoscopy has proven to be effective in reducing the number of adenomas in Chinese patients with FAP (81,82).

7. Roles of TCM

For Chinese patients with FAP who do not consent to surgical intervention or chemotherapy, TCM is an available option. In 1995, An *et al* (83) reported that 15 patients diagnosed with CFAP receiving TCM through oral administration and retention enema exhibited a reduction in clinical CFAP symptoms, including diarrhea and hematochezia. Furthermore, Huo *et al* (84) reported the case of a patient with CFAP who rejected surgical treatment and who, following 3 years of regular treatment with TCM, had only a single polyp identified by endoscopic evaluation.

8. Conclusions

Previously, the majority of patients with FAP in China were identified in the late stages of the disease, presenting with bowel obstructions, rectal bleeding or adenocarcinomas (5). Due to the poor prognosis and genetic diversity of FAP, clinicians and geneticists in China have studied the disease for the past three decades (5-10).

According to PubMed and multiple Chinese databases, cases of FAP among the Chinese population are mainly of the subtype CFAP. The colonic manifestations of these patients are typically easy to diagnosis (11), and extra-colonic manifestations, including CHRPE, are indicators of CFAP (12). Patients presenting with fewer adenomas (18,19) are now increasingly recognized as having a separate subtype of FAP, known as AFAP, and are studied separately. However, cases of MAP in China remain rare (44).

FAP is an autosomal dominant disease (1,13); mutations of the APC gene are considered to be the main causes of CFAP and AFAP (18,19), and mutations of the MUTYH gene are

associated with MAP (20-23). However, the FAP genotype varies significantly between countries (26-33). FAP in China has its own characteristics; the mutation spectrum of the APC gene in China is not consistent with the mutation spectrum of FAP in Western countries (5,34-36). The MCR of APC in Chinese patients localizes to exon 16, between codons 849 and 1376, whereas the MCR of APC in Western patients is reported to localize between codons 1250 and 1464 (50-51). In addition, mutations of APC gene polymorphisms are frequently located between codons 1309 and 1061 in Chinese patients with FAP, which is consistent with polymorphisms identified in Western countries (57). Other APC polymorphisms frequently observed include, c.4393_4394delAG at codon 1465, c.4012C>T at codon 1338 and c.994C>T at codon 332. As reports of MAP in the Chinese population are few in number, the frequent MCR polymorphisms in the MUTYH gene remain unclear (44). Additionally, a large subset of Chinese patients with FAP have undetectable pathogenic mutations. The rate of APC(-) and MUTYH(-) in China ranges between 30 and 60% depending on the province (62,63). There are 56 ethnic groups in China, and living conditions vary between provinces (85), which may affect the genetic diversity of FAP in China.

Surgical intervention and chemotherapy has been proven to benefit patients with FAP (64,65,72,73). In China, laparoscopic IPAA surgery is considered the standard treatment for patients diagnosed with CFAP and advanced AFAP (66,67). Due to rapid progress in colonoscopy, doctors in China are able to remove the numerous adenomas using endoscopic polyp electrocution and endoanal mucosal stripping (69,70). Celecoxib is the recommended FAP chemotherapeutic used to delay the development of adenomas into adenocarcinoma and prevent the recurrence of adenomas. Furthermore, combined celecoxib treatment and endoscopy has been proven to effectively reduce the number of adenomas in patients with FAP (81,82).

For Chinese patients with FAP who do not consent to surgical operation, TCM is another option and has been used in the treatment of colonic disorders (86). Having developed over thousands of years, TCM is considered to be a complete system of healthcare and includes a complex herbal therapeutic component (87). Following treatment with TCM, patients with FAP have exhibited long-term survival and reduced colorectal symptoms, which provides evidence for the use of Chinese herbal medicine in the successful prevention and treatment of FAP (83,84). Researchers in China are attempting to study the active ingredients of traditional herbal therapeutics and elucidate their mechanism of action (86,88). However, further randomized controlled trials on TCM are required.

In conclusion, as the understanding of genotype-phenotype correlations between FAP subtypes increases, patients diagnosed with FAP in China are gradually benefiting from improved surgical intervention, colonoscopy, chemoprevention, surveillance and TCM. However, multiple characteristics of FAP remain unclear. There is a significant number of patients diagnosed with FAP but with no identified genetic mutation, even following sophisticated genetic testing (41,42,44); due to this many high-risk individuals may be misdiagnosed. There is clinical evidence to support the possibility of influencing the manifestation of FAP through chemoprevention and lifestyle changes (72,73). There are

certain clinical cases showing the efficacy of TCM in the treatment of FAP, however the active ingredient remains to be elucidated. Therefore, the mechanisms of FAP require further research and evaluation.

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