

Singapore Familial Adenomatous Polyposis (FAP) Patients with Classical Adenomatous Polyposis but Undetectable *APC* Mutations Have Accelerated Cancer Progression

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OBJECTIVES: Germline mutation in adenomatous polyposis coli (*APC*) is detected in up to 80% of familial adenomatous polyposis (FAP) patients worldwide. In this study, we evaluated clinical features and *APC* mutations of Singapore FAP patients and contrasted genotype–phenotype correlation with Caucasians from other regions of the world and between FAP patients with and without detectable *APC* mutations.

METHODS: We screened 242 members from 57 unrelated FAP families using a combination of cDNA protein truncation test, multiplex ligation-dependent probe amplification, and differential expression techniques.

RESULTS: *APC* germline mutations were detected in 50 families. In contrast to Caucasians, fundic gland polyposis in Singapore patients was associated with *APC* mutations throughout the coding region and osteomas were also not confined to codon 767–1573. There was also no FAP-associated hepatoblastoma or medullablastoma. *APC* mutation-negative patients from four families with mixed (adenomatous/hyperplastic/atypical juvenile) polyps were subsequently reclassified as hereditary mixed polyposis syndrome (HMPS) patients. *APC* mutation-negative patients with classical adenomatous polyposis were negative for *MYH*, β -catenin, and *Axin 1* mutations. These patients had a significantly older age at diagnosis ($P < 0.001$) and more colorectal cancers ($P = 0.017$) than patients with *APC* mutations.

CONCLUSIONS: We achieved a 94% (50/53) *APC* mutation detection rate via a combination of techniques, suggesting that the current detection rate is probably not exhaustive. Singapore patients have some features similar to and other features distinct from Caucasians. Furthermore, *APC* mutation-negative patients have accelerated cancer progression that merits closer surveillance.

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INTRODUCTION

Familial adenomatous polyposis (FAP), an autosomal dominantly inherited form of colorectal cancer (CRC), is characterized by the appearance of hundreds to thousands of adenomatous polyps in the colon and rectum of affected individuals in the second or third decade of life. If left untreated, one of these polyps is bound to progress to cancer, that is, the penetrance of the disease is virtually 100%. Germline mutation in the adenomatous polyposis coli (*APC*) gene on chromosome 5q21 was found to be the underlying defect for FAP (1–3). Subsequently, inactivation of *APC* was also found to be an early event in the majority of sporadic CRC cases (4). Nevertheless, 20–50% of FAP patients worldwide were reported to have no detectable *APC* mutations (5–8).

Attenuated FAP is a less severe form of FAP, in which patients manifest with less than 100 polyps at a later age. Some attenuated FAP patients have been found to have germline mutations in the extreme 5' and 3' ends of *APC* (9, 10). In

recent years, biallelic mutations in the base excision repair gene, *MYH*, have been detected in a small proportion of attenuated FAP patients with no detectable *APC* mutations (11–13). However, *MYH* mutation has hitherto not been reported in FAP patients with clear autosomal dominant inheritance and classical polyposis (more than 100 polyps).

In this study, we screened 242 members of 57 unrelated FAP families registered with the Singapore Polyposis Registry for *APC* germline mutation exhaustively, using a combination of techniques. This enabled us to genotypically and phenotypically characterize FAP patients with and without *APC* mutations for comparative studies and for the search for other causative mutations.

MATERIALS AND METHODS

Samples

Eighty FAP families are registered with the Singapore Polyposis Registry. Peripheral lymphocyte specimens were

available for 242 members of 57 unrelated FAP families. All probands were diagnosed at colonoscopy or colectomy. The diagnostic criterion for FAP was the presence of 100 or more adenomas throughout the colon and rectum as documented in the patient's histopathological records. The proband was interviewed by the coordinator of the Singapore Polyposis Registry, and a detailed pedigree of the family and clinical history of other affected members were documented. Patients under 50 years of age at diagnosis whose cancer was associated with at least 20 but less than 100 adenomas and whose pedigree showed clear autosomal dominant inheritance were included as attenuated FAP patients. This study was approved by the Ethics Committee of Singapore General Hospital, Singapore.

DNA/RNA Extraction

DNA was obtained from peripheral blood lymphocytes by a simple salting out procedure (14). RNA extraction was performed from fresh blood lysates using the Promega (Madison, WI) Total RNA isolation kit according to the manufacturer's protocol.

PTT Assay

The *APC* coding region of the human gene (Genebank accession number M73548) was amplified by six overlapping PCR/RT-PCR segments as previously described (15). The overlap was at least 450 nucleotides to ensure that no truncation at the ends of the segments was missed. The unpurified PCR product was *in vitro* transcribed and translated into protein with the TNT/T7-coupled reticulocyte lysate system (Promega). The size of the truncated protein was used to estimate the mutation site. The relevant PCR fragments were identified and primers were selected for PCR-based BigDye dideoxy sequencing using an ABITM 310 automated sequencer (Applied Biosystems, Foster City, CA).

Multiplex Ligation-Dependent Probe Amplification (MLPA)

Large deletions in *APC* were screened for using the MLPA test kit (SALSA P043 *APC* exon deletion test kit, MRC, Holland) according to manufacturer's protocol. The kit contains 23 probe sets from the *APC* region comprising three promoter regions, exons 1–14, 3 fragments of exon 15 (15-s, 15-m, 15-e), fragments containing the alternatively spliced and frequently mutated sites of exon 10A (A), codon 1061 (B), and codon 1309 (C). Probe sets from other chromosomal regions were included as controls. Briefly, 100 ng of genomic DNA in 5 μ L TE buffer was heat denatured and incubated with the SALSA probe mix for 16 h at 60°C. Hybridized products were then ligated, amplified by PCR, and separated on an ABI 3100 sequencer. The Genescan and Genotyper software programs were used for data collection and export. Evaluation of electropherograms was performed by visual examination of peak heights of the *APC* fragments in relation to adjacent control fragments compared with samples from normal healthy individuals.

Differential Expression Analysis

Two-site polymorphisms with silent changes of a single base pair, one in codon 486 TAC/T (exon 11) and one in codon 545 GCA/G (exon 13) of *APC*, were used. Informative heterozygous cases were first determined by analyzing amplified exons 11 and 13 from genomic DNA. Differential expression in mRNA was then examined by comparing the sequence of the PCR-amplified fragments containing the polymorphic sites from genomic DNA with cDNA.

MYH, β -Catenin, and Axin 1 Mutation Screening

MYH cDNA was amplified into two overlapping segments corresponding to codon 1–610 and codon 540–1137 and sequenced with 8 primers at 450-bp intervals. β -catenin exons 2–4 from genomic DNA and RNA were PCR or RT-PCR amplified and sequenced directly to search for genomic rearrangement or missense mutation at the serine/threonine residues in exon 3, the putative GSK-3 β phosphorylation sites. Similarly, to search for germline mutation in *Axin 1*, a set of primers encompassing the whole coding region for RT-PCR and nested PCR experiments and a series of internal primers for direct sequencing were designed. The primers and RT-PCR and nested PCR conditions are available on request.

Statistical Analysis

The χ^2 and Fisher's exact tests were used to evaluate the statistical significance of clinical variation between patient groups. Differences were taken as significant when the *P* value (2-tailed) was less than 0.05.

RESULTS

Identification and Characterization of *APC* Mutations

We screened the entire coding region of *APC* with a cDNA protein truncation test (cDNA-PTT) for germline mutations in 242 members of 57 unrelated FAP families, and found truncated proteins in 46 families. We confirmed the mutations by DNA sequencing and identified 33 different mutations (Table 1). These include 10 nonsense mutations, 18 small deletions and insertions, 3 splicing mutations, and 2 genomic (exonic) deletions (16). Nineteen patients from four families were reclassified as hereditary mixed polyposis syndrome (HMPS) patients (17) because of the presence of mixed adenomatous, hyperplastic, and atypical juvenile polyps (Table 3).

For the remaining seven families, we performed MLPA, which identifies large deletions undetectable by PTT. Genomic deletions were found in three families (Table 1, Fig. 1). Two families had whole *APC* gene deletions, from the promoter to the 3' untranslated regions (UTR). One family had a deletion that begins at the 3' end of exon 15 of *APC*.

In order not to miss any mutation resulting in differential expression in the remaining four families, we amplified fragments from both the genomic DNA and RNA containing the

Table 1. APC Germline Mutations and Phenotypic Spectrum of Singapore FAP Patients

FAP Family	Exon	Position	Mutation Description	Mutation Type	Extracolonic Manifestation
45 (2)	4	170	ATAGATAGTC → ATAGTC	Deletion	
78 (3)	5	213	CGA → TGA	Nonsense	Desmoid
9 (4), 77 (1)	6	232 [†]	CGA → TGA	Nonsense	Duodenal polyps, FGP
14 (6)	8	299 [†]	ACTCTG → ACTG	Deletion	Desmoid, FGP
76 (1)	8	302	CCTCGA → CCTTGA	Nonsense	Desmoid
28 (2)	9	332 [†]	CGA → TGA	Nonsense	
74 (1)	9a	430	GGC^atggac^CAG → GGCTcatgaacataCAG	Indel	
5 (4)	11	470* [†]	tttaaattag/GGG → ttttag/attagGGG (ATTAG insertion)	Splicing	CHRPE, osteomas
21 (1)	11	510*	ACTTTTIG → ACTTTG	Deletion	
11 (4)	14	Intron 13 [†]	ctag/GAA → ctgg/GAA (exon 14 deletion)	Splicing	CHRPE, stomach cancer, FGP
75 (2)	14	581*	Skip exon 14 tactag/GAATC → tactag/TAATC	Splicing	
34 (7)	15	674* [†]	ATAGTTTGACAATAGTCAG → ATAGTCAG	Deletion	CHRPE, cyst, desmoid
71 (1)	15	805	CGA → TGA	Nonsense	Duodenal cancer
44 (2)	15	831* [†]	TTA → TTAA	Insertion	
72 (1)	15	887*	ATTGCC → ATGCC	Deletion	Duodenal polyps
13 (2), 51 (3)	15	935 [†]	TAC → TAA	Nonsense	CHRPE, thyroid cancer, desmoid
7 (3)	15	938* [†]	ACTAAG → AG	Deletion	
48 (2)	15	974*	GGT → GT	Deletion	
62 (1)	15	1038*	TCTGGAA → TCGAA	Deletion	
23 (1), 56 (2)	15	1061	AAACAAGT → AAGT	Deletion	Desmoid, FGP
60 (1)	15	1062	CAAAGT → CAGT	Deletion	Desmoid, FGP
57 (1)	15	1067	CAA → TAA	Nonsense	Cyst
1 (4), 10 (1), 18 (3), 19 (1), 25 (3), 27 (5), 32 (2), 39 (1), 49 (1), 55 (3)	15	1309 [†]	AAAGAAAAGATT → AAAGATT	Deletion	CHRPE, osteomas, duodenal polyps, FGP, cyst, desmoids
33 (1)	15	1343* [†]	TCT → TT	Deletion	
16 (2)	15	1428* [†]	GGA → GG	Deletion	
54 (1)	15	1441*	CCACCT → CCAACCT	Deletion	FGP
52 (1)	15	1450	CGA → TGA	Nonsense	Osteomas, desmoid, FGP
15 (3)	15	1465*	(AG) ₅ → (AG) ₆	Insertion	CHRPE, duodenal polyps, FGP, desmoid
61 I:1	15	1465	(AG) ₅ → (AG) ₄	Deletion	Desmoid
69 (2), 73 (1)	15	1480*	CAG → TAG	Nonsense	Desmoid, osteomas
50 (1)	15	1503* [†]	TCA → TAA	Nonsense	Desmoid, FGP
4 (16)	11	Intron 10–11* [†]	Delete E11 (2 kb)	Genomic deletion	CHRPE, FGP, thyroid cancer, desmoid
35 (2)	14	Intron 13–14* [†]	Delete E14 (6 kb)	Genomic deletion	
67 (1)	15	3'	Incl. 3' UTR	Genomic deletion	FGP
6 (1)	1–15		Incl. P, 5' and 3' UTR	Genomic deletion	Desmoid, thyroid, and ovarian tumors
22 (4)	1–15		Incl. P, 5' and 3' UTR	Genomic deletion	CHRPE, nasopharyngeal cancer
58 (3)	11, 13	486, 545	TAC/T → TAC; GCA/G → GCA	Monoallelic expression	

The number of patients is shown in parentheses after family ID. *Novel mutation; 17/37 mutations novel; [†]Mutation previously published in Eur J Hum Genet 2000; 8: 42–8. CHRPE = congenital hypertrophy of the retinal pigment epithelium; FGP = fundic gland polyposis.

polymorphic sites at codon 486 and 545 and sequenced the fragments. In one family, heterozygosity at both polymorphic codons (C/T at codon 486 and A/G at codon 545) was found in the genomic DNA, but monoallelic expression was

detected at both sites (C at codon 486 and A at codon 545, Fig. 2) in the cDNA. This indicates that a mutation has caused low or no expression of one of the two APC alleles. The other three families show heterozygosity at codon 486 at both the

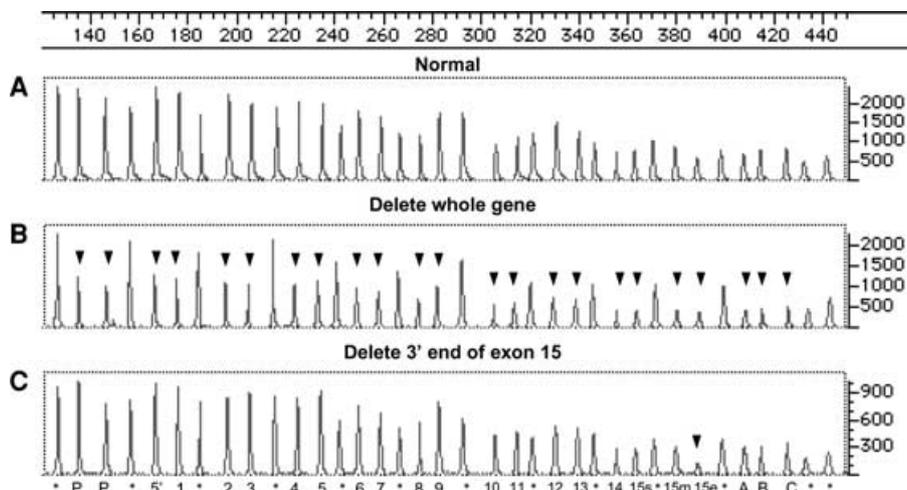


Figure 1. Electropherograms of MLPA products showing (A) a normal control, (B) a deletion of the whole *APC* gene, and (C) a deletion at the 3' end of exon 15.

genomic DNA and cDNA level, suggesting that no mutation has caused monoallelic expression.

The probability of finding a missense mutation among 53 families is very low, as less than 2% of *APC* germline mutations are missense mutations (18). Despite this, we screened for I1307K, E1317Q, A290T, C358T, and A8822G, putative pathologic missense mutations in other populations (19), in the remaining three families by direct sequencing analysis. None of these missense variants were detected in any of the probands of the remaining families.

In total, *APC* germline mutations were detected in 50 of 53 FAP families (Table 1, Fig. 3). Some of these mutations have been previously reported (20).

MYH, β -Catenin, and Axin 1 Mutation Screening

Next, we screened the entire *MYH* coding region for germline mutation in probands of the three families without detectable *APC* mutations. No *MYH* mutation was detected in any of the probands. At the mutational hot spots (codons 165 and 382) for Caucasians (11–13), the normal codons (Y and G) were detected in all three probands.

In addition, we amplified the genomic DNA and RNA fragments encompassing exon 3 of β -catenin for germline mu-

tations. No mutation in β -catenin was found (15). Furthermore, sequencing the entire coding region of *Axin 1* revealed no germline mutation in *Axin 1* in any of the probands of the remaining families.

Phenotypic Comparison of FAP Patients with and without *APC* Mutation

Thirteen patients from the three FAP families without detectable *APC* mutations had numbers of adenomatous polyps that are typical for patients with detectable *APC* mutations (Table 2). However, they had distinct features. The phenotypic features of *APC* mutation-negative patients were compared with those of the *APC* mutation-positive patients.

The mean age at diagnosis for FAP patients with detectable *APC* mutations was 30.1 yr, with a majority (63%) of the patients diagnosed in the 20–39 age group (Table 3). The mean age at diagnosis of FAP patients without *APC* mutations (47 yr) was significantly older than the age at diagnosis of patients in the *APC* mutation-positive group ($P < 0.001$, Table 3). The majority of these patients (66%) were diagnosed in the 30–49 age group, which was a decade later than the majority (63%) of the patients with detectable *APC* mutations.

Notably, however, the incidence of CRC in *APC* mutation-negative patients (85%) was significantly higher ($P = 0.017$, Table 3) than the incidence of CRC in *APC* mutation-positive patients (47%). The incidence of synchronous CRC in patients without *APC* mutations (27%) was also higher than that in patients with *APC* mutations (11%), although it did not reach statistical significance.

There was no significant difference in the sex ratio or incidence of all extracolonic manifestations (ECM), upper gastrointestinal (GI) polyps, or desmoids between the two groups (Table 3).

The characteristics of the HMPS patients are included in Table 3 for comparison purposes.

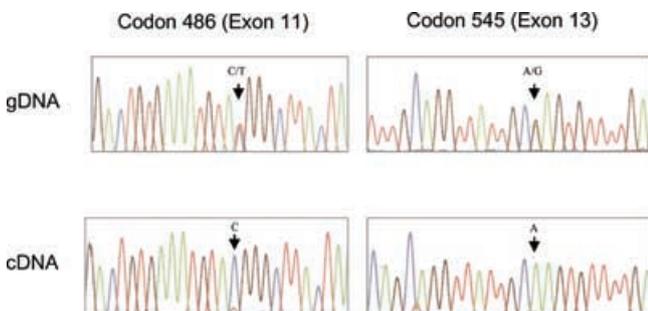


Figure 2. Monoallelic expression of codons 486 (TAC/T) and 545 (GCA/G) in mRNA of proband of family 58.

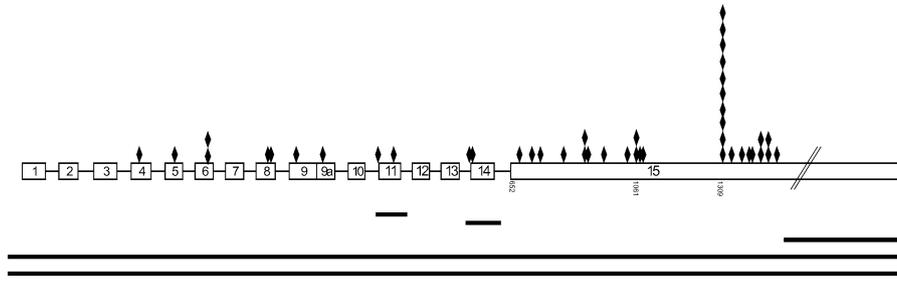


Figure 3. Mutation spectrum for the entire *APC* coding region. Each diamond symbol indicates one FAP family with a germline mutation at a particular position. Codon 1309 in exon 15 is the “hot spot” with 10 FAP families. Solid lines below the exon and the whole coding region indicate genomic deletions involving the exon and the entire coding region, respectively.

DISCUSSION

Using a combination of cDNA-PTT, MLPA, and differential expression techniques (Figs. 1–3), we successfully detected *APC* germline mutations in 50 of 53 FAP families (94%). This detection rate is considerably higher than the prevailing frequencies (50–80%) reported worldwide (5–8). It corroborates the rate reported in one previous study using a combination of PTT and the much more time- and cost-consuming monoallelic mutation analysis (MAMA) approach (21), suggesting that this higher detection rate probably better reflects the true *APC* mutation rate in FAP patients.

Thirty-seven different *APC* mutations were found in 50 FAP families, confirming mutation heterogeneity in *APC* (Table 1). All mutations resulted in the loss of either one or both of the β -catenin binding sites and, except for the mutation at codon 332 (in the alternative spliced site of exon 9), resulted in classical polyposis. More than one-third of the mutations were found with cDNA analysis. Thus, nonsense-mediated decay of the truncated transcript does not appear to be a problem for *APC* mutation screening.

About two-thirds of the FAP families (34/53) in this study are Chinese of Han origin. Eleven (21%) of the families are

Malay families and the rest of the families (15%) are of Indian, Eurasian, and foreign origins. Thus, FAP families in this study are representative of the South East Asian population by ethnic composition. It is thus interesting to compare the *APC* mutations and genotype–phenotype correlation of these families with those reported for other populations. Like the Caucasian families (22), the 5-bp deletion at codon 1309 is the hot spot for the local families (Fig. 3). Although 10 families (20%) have this same mutation at codon 1309, it is unlikely that there is a founder population, because three of these families have *de novo* mutations and the remaining families are from two different ethnic groups (five Chinese families of different family names and two Malay families). However, unlike the Caucasian families (22), mutation at codon 1061 (2/50 families) was not the second hot spot for the South East Asian population.

Five genomic deletions (10%) were found, which is consistent with the latest frequency (12%) reported for *APC* in the Caucasian population (7, 23), confirming that large deletions are not rare in FAP. Two of the genomic deletions were exonic deletions in exon 11 and 14 (Table 1), resulting in truncated proteins and classical polyposis (16). However, patients from three families with three different genomic deletions (two

Table 2. Phenotypic Spectrum of FAP Patients Without Detectable *APC*/ β -Catenin/*Axin 1* Germline Mutations

FAP Family	FAP Patient	Age at Diagnosis and Sex	Colonic Manifestation		
			Polyps	Cancer (Duke’s Stage)	Extracolonic Manifestation (age)
29	I:1	22 F	N.A.		Breast cancer (22)
	II:1	52 F	N.A.		
	II:2	? F	N.A.	+ (?)	
	II:3	47 F	>100	+ (C) 3 Synchronous	
	II:5	44 F	N.A.	+ (?)	
	II:6	44 F	<100	+ (C) 6 Synchronous, mucinous	
	III:3	32 F	>100		
30	I:1	? F	N.A.	+ (?)	CHRPE, epidermal cyst (34); desmoid (37) Desmoid (44)
	II:4	36 M	>100	+ (B)	
	II:5	42 F	>100	+ (C) 3 Synchronous	
36	I:1	60 M	N.A.	+ (?)	Breast cancer (48) Fundic polyps (35)
	II:1	67 M	N.A.	+ (?)	
	II:3	60 M	N.A.	+ (?)	
	II:5	? F	N.A.		
	III:2	33 F	>100	+ (A)	

Table 3. Phenotypic Comparison Between *APC* Mutation-Positive and Negative FAP and HMPS Patients

	FAP		HMPS	<i>P</i> Value*
	<i>APC</i> Mutation Positive	<i>APC</i> Mutation Negative		
Patients/Family	122/50	13/3	19/4	
Sex ratio (Male/Total)	65 (53%)	4 (31%)	12 (63%)	0.151
Avg. age at diagnosis	30.1	47	34.8	0.000
Polyps	100–1,000s	100–1,000s	<100	
Mixed polyps [†]	No	No	Yes	
Colorectal cancer (CRC)	57 (47%)	11 (85%)	9 (47%)	0.017
Synchronous CRC	6 (11%)	3 (27%)	0 (0%)	1.000
ECM [‡]	69 (57%)	4 (31%)	3 (16%)	0.087
Upper GI polyps [§]	23 (19%)	1 (8%)	0 (0%)	0.463
Desmoids	20 (16%)	3 (23%)	0 (0%)	1.000
Breast cancers	No	Yes	No	

**P* value based on statistical calculations between patients of the *APC* mutation-positive and *APC* mutation-negative groups.

[†]Mixed adenomatous, hyperplastic, and atypical juvenile polyps. [‡]Extracolonic manifestation. [§]Upper gastrointestinal (duodenal and fundic gastric) polyps.

whole gene deletions and one deletion from the 3' end of exon 15 of *APC*) also exhibited classical rather than attenuated polyposis. This finding corroborates the finding in the Caucasian population (5, 6, 23) and supports the model that haploinsufficiency can result in classical polyposis. Notably, two patients from the two families with whole gene deletions were also diagnosed with ovarian and nasopharyngeal cancers 10 and 4 yr after the diagnosis of FAP at age 42 and 44, respectively. These are not cancers commonly associated with FAP in the Caucasian population (8, 22).

The mean age at diagnosis and frequencies of all ECM, upper GI polyps, and desmoids for patients with detectable *APC* mutations were similar to those reported for Caucasian populations (Tables 1 and 3). The 3' hot spot for desmoids (codon 1445–1580) for the Caucasian families (24) was also the hot spot for the local families, with six of nine patients (67%) manifesting with desmoids. A second hot spot for desmoids was found in exon 8, with four of seven patients (57%) documented with desmoids. Nevertheless, three of the patients were from the same family, and thus it is unclear whether this is a result of a shared environmental factor or the *APC* mutation site. CHRPE was the only ECM with no intrafamily variation. Surprisingly, we found three families (Table 1) that do not conform to the CHRPE domain (codon 463–1387) prescribed for the Caucasian population (24, 25). This demonstrates that the correspondence to the prescribed CHRPE domain is not absolute. Fundic gland polyposis was associated with *APC* mutations throughout the coding region and not predominantly after codon 1456, as reported for Caucasians (26). Osteoma was also not confined to mutations from codon 767–1513, as in the Caucasian population (27). There was also no FAP-associated hepatoblastoma or brain cancer documented for the local FAP patients, suggesting that, in contrast to Caucasians (8, 28), these manifestations are rare in South East Asian populations.

Two previous studies (29, 30) on Caucasian populations have reported that the age at diagnosis of FAP patients without detectable *APC* mutations was significantly older than for patients with *APC* mutations; while a more recent study

(26) had a contradictory observation. In this study, we also found the age at diagnosis of patients without *APC* mutations to be significantly older than that of patients with *APC* mutations (Table 3). Our series thus concurs with the findings of these two earlier studies. However, we found that FAP patients without detectable *APC* mutations had higher frequencies of CRC and synchronous cancers than patients with *APC* mutations, which is consistent with them having a more severe phenotype, as reported by the third study (26). One patient, for instance, presented with six synchronous carcinomas at age 44. Notably, in all three earlier studies, there was no attempt to exclude patients with mixed polyposis, which clearly had a different etiology from adenomatous polyps alone (17, 31). In this study, HMPS patients were excluded from the statistical analysis between FAP patients with and without *APC* mutations (Table 3). Patients with no clear autosomal dominant inheritance and less than 100 polyps were also excluded for separate *MYH* screening.

An additional finding, which was not reported in all three earlier studies, is the association with breast carcinomas in two of the *APC* mutation-negative families but not in any of the 50 families with *APC* mutations. In fact, the proband of family 29 was only diagnosed with breast carcinoma when she died of complications arising from twin delivery at age 33. Five of her six daughters and one of her granddaughters, however, were subsequently diagnosed with FAP. Individual II:5 of family 36 was diagnosed with breast cancer at age 48 but not CRC. This observation suggests the possibility that the causative gene whose mutation mimics the inactivation of *APC* may also be involved in an alternative pathway that gives rise to breast carcinomas.

In conclusion, we achieved a high *APC* mutation detection rate of 94% via a combination of cDNA-PTT, MLPA, and differential expression techniques. Genotypic and phenotypic characterizations indicate that South East Asian families have some features similar to and other features distinct from Caucasian families from other regions of the world. FAP patients without detectable *APC* mutations display unique features that are different from patients with *APC* mutations. Although

the *APC* mutation-negative group had a significantly older age at diagnosis, tumorigenesis appears to progress faster, resulting in a higher cancer incidence and multiple cancers. This accelerated progression and association with breast carcinomas have to be considered for clinical management and when counseling family members. Considering the retrospective nature and limited number of *APC* mutation-negative patients in this study, however, these observations would need to be replicated in other centers with larger numbers of cases.

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STUDY HIGHLIGHTS

What Is Current Knowledge

- The adenomatous polyposis coli (*APC*) detection rate in familial adenomatous polyposis (FAP) worldwide is up to 80%.
- FAP genotype–phenotype correlation has been reported in Caucasians.
- *APC* mutation-negative FAP patients are not well defined.

What Is New Here

- The *APC* detection rate in FAP is 94%.
- Genotype–phenotype correlation is reported in South East Asians and contrasted with Caucasians from other regions of the world.
- *APC* mutation-negative patients have accelerated cancer progression.

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CONFLICT OF INTEREST

The authors indicate no potential conflicts of interest.
