Short Communication

Serrated Adenomas Have a Pattern of Genetic Alterations That Distinguishes Them from Other Colorectal Polyps

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Abstract

Background: **Serrated adenomas are characterized by serrated crypts with dysplasia, and are distinguished from other polyps by their histology, but the genetic basis of serrated adenomas is unknown. We investigated genetic alterations in colorectal polyps to determine if a specific pattern were associated with serrated adenomas.**
Methods: **Sixty-six small (<10 mm) colorectal polyps were studied, including 11 hyperplastic polyps, 27 serrated adenomas, 9 tubular adenomas, 6 tubulovillous adenomas, and 3 villous adenomas. Allelic imbalance and microsatellite instability were detected by analysis of microsatellites on 5q, 18q, 17p, 2p, and 3p; K-*ras* mutations were detected by oligonucleotide hybridization.**
Results: **Each polyp subset had its own characteristic mutational signature. Allelic imbalance of 18q was significantly more common ($P < 0.05$), whereas allelic imbalance of 5q and K-*ras* mutations were significantly less common ($P < 0.05$) in serrated adenomas compared with other polyps. Allelic imbalance of 17p was not found in any polyp.**
Conclusions: **Serrated adenomas are significantly more likely to have allelic imbalance at 18q than other types of adenomas, and significantly less likely to have allelic imbalance at 5q or K-*ras* mutations. Serrated adenomas seem to evolve through a different genetic pathway than other types of polyps in the colon.** (Cancer Epidemiol Biomarkers Prev 2005;14(9):2253–6)

Introduction

Colorectal neoplasms result from the sequential accumulation of alterations in genes that regulate cell growth. These alterations include activating point mutations of K-*ras* (1) and inactivation of several tumor suppressor genes, most notably the *APC* gene on chromosome 5q21 (2), the *p53* gene on 17p13 (3), and one of several candidate tumor suppressor genes on chromosome 18q, most likely *DPC4/SMAD4* (4). Different patterns of genetic alterations in tumor suppressor genes, DNA mismatch repair genes, and K-*ras* have been correlated with distinctive phenotypes of colorectal cancer, precursor neoplasms, and other polypoid lesions in the colon (5, 6).

It is currently appreciated that colorectal neoplasia may evolve through one of several different genetic pathways (7). Not all colonic polyps have the same malignant potential. Adenomatous polyps are the classic precursors of colorectal cancer, but other lesions, such as hyperplastic polyps are thought not to have a propensity for such evolution.

Serrated adenomas are polypoid lesions present in the colon that are characterized by saw-toothed or serrated crypts with dysplasia, and are distinguished from classical adenomas and hyperplastic polyps by their histologic appearance (8). Serrated adenomas were recognized as a distinct entity in 1990, and have also been referred to as mixed hyperplastic adenomatous polyps (9). It has been reported that serrated adenomas make up ~1% to 2% of all colorectal polyps (10). Serrated adenomas have been reported to have infrequent mutations of *APC* (11), frequent methylation of the promoters of putative tumor suppressor genes (12), and other genetic alterations (13). There has not been a systematic search for patterns of genomic instability in these lesions, and the relevance of these lesions to a multistep carcinogenesis pathway remains uncertain. In this study, we tested the hypothesis that serrated adenomas might have a unique mutational spectrum compared with other types of lesions in the colon, which could provide insight into the biological basis and clinical potential of these lesions.

Materials and Methods

Patients. A total of 66 small sporadic colorectal polyps, all from different individuals and <10 mm in diameter, were obtained for this study. Eleven lesions were hyperplastic polyps, and 55 were various adenomatous polyps including 27 serrated adenomas, and 28 other types of adenomas (19 simple tubular adenomas, 6 tubulovillous adenomas, and 3 villous adenomas); all were excised endoscopically at the Karolinska Hospital, in Stockholm, Sweden.

DNA Extraction. DNA was extracted from 10% buffered formalin-fixed, paraffin-embedded tissue sections. Genomic DNA was isolated from the excised microdomain pellets as previously described (5).

K-*ras* Mutation Analysis. The DNA was amplified by two-step PCR. PCR amplification of exon 1 of a K-*ras* fragment containing codons 12 and 13 was first done by the following primers: forward 5′CGTCCACAAAATGATTCTGAATTAGC-TGTATC3′; reverse 5′CCTTATGTGTGACATGTTCTAATA-TAGTCAC3′. Thirty-five cycles (92°C for 30 seconds and 67°C for 30 seconds) were done followed by a 10-minute extension at

Received 10/27/04; revised 5/25/05; accepted 7/19/05.
Grant support: NIH (R-01 CA72851) to C.R. Boland.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked advertisement in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
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doi:10.1158/1055-9965.EPI-04-0790

72°C. The initial PCR products were diluted and further amplified with hemi-nested primers: forward 5′AGGCCTGCT-AGGCCTGCTGAAAATGAC3′; reverse, the same primer as described above. Thirty-five cycles of amplification (92°C for 25 seconds, 55°C 25 seconds, and 72°C for 25 seconds) were done followed by a 10-minute extension at 72°C. The amplified DNA fragments were then dot-blotted onto nylon filters (Hybond-N, Amersham, Buckinghamshire, United Kingdom) and hybridized with radiolabeled oligomer probes for all possible mutations of codon 12 and the GAC mutation of codon 13.

Assays for Allelic Imbalance and Microsatellite Instability. The DNA was amplified by PCR using 5′ ^{32}P-end labeled primers using multiple microsatellite markers at microsatellite loci linked to *APC* on 5q, *DPC4/SMAD4* on 18q, *p53* on 17p, and the DNA mismatch repair genes *hMSH2* on 2p and *hMLH1* on 3p as previously described (5). PCR reactions were carried out as previously described, and repeated at least twice to ensure that the results were reproducible in each case.

Assessment of allelic imbalance (also called loss of heterozygosity or LOH) was assigned when a tumor allele showed at least a 50% reduction in the relative intensity of one allele in neoplastic tissue compared with matched normal DNA. Microsatellite instability (MSI) was defined by band shifts at two or more microsatellite loci, which is MSI-high, or MSI-H (14). Band shifts in only one of the markers was defined as MSI-L. Samples with MSI were not considered informative at that locus for the LOH analyses. Similarly, if only one band were produced at PCR in the normal tissue, these samples were not informative for that locus for assessing allelic imbalance/LOH, although these were potentially useful for MSI analysis.

Statistical Analysis. Comparisons between the two groups were done by Fisher's exact test using the statistical software package StatView. P values ≤ 0.05 were considered statistically significant.

Results

Histologic Analysis. Serrated adenomas were characterized by saw-toothed, elongated, and dilated crypts with nuclear atypia. Hyperplastic polyps also showed saw-toothed and dilated crypts and were distinguished from serrated adenomas by the absence of significant nuclear atypia.

K-*ras* Mutations. K-*ras* mutations were detected by dot-blot hybridization of PCR products, and confirmed by direct sequencing. The genetic alterations in all 66 colorectal polyps are summarized in Table 1. Tables 2 and 3 provide details of the genetic alterations identified in 27 serrated adenomas and 11 hyperplastic polyps, respectively. As shown in Table 1, serrated adenomas had significantly fewer K-*ras* mutations (2 of 27; 7%) compared with the other adenomas (10 of 28; 36%; $P = 0.011$, Fisher's exact test). In contrast, no significant difference was found between lesions with low-grade dysplasia versus high-grade dysplasia. Four of 11 (37%) hyperplastic polyps had K-*ras* mutations, which is the same as that found in nonserrated adenomas (36%). K-*ras* mutations were significantly associated with an exophytic appearance of an adenoma ($P = 0.029$).

Allelic Imbalance/LOH at Tumor Suppressor Gene and DNA Mismatch Repair Gene Loci. Allelic imbalance or LOH at 18q was significantly more frequent in serrated adenomas than in other adenomas ($P = 0.046$), being found in 7 of 25 (28%) and 2 of 27 (7%) informative serrated adenomas and other adenomas, respectively. LOH at 5q was not found in any serrated adenoma, but was present in 6 of 28 (21%) other adenomas ($P = 0.016$). LOH at 2p (*hMSH2*) was found in 3 of 23 informative serrated adenoma, but LOH at 2p was not found in other adenomas. LOH on 3p (*hMLH1*) was found in 5 of 23 and 3 of 24 informative serrated adenomas and other adenomas, respectively. LOH at the DNA mismatch repair genes was not significantly different between any adenoma types. LOH at 17p (*p53*) was not found in any informative case, as expected (15). Hyperplastic polyps had LOH at 3p (2 of 10) and 18q (2 of 10), but no LOH at 2p, 5q, and 17p. No significant difference was found in the frequency of LOH on each locus between nuclear grades.

Microsatellite Instability. We identified MSI-H in 1 of 27 (4%) of the serrated adenomas, 0 of 28 other adenomas, and 0 of 11 of the hyperplastic polyps. MSI-L was identified in 11 of 27 (41%) of the serrated adenomas, and 11 of 28 (39%) other adenomas. Five of the 11 (45%) hyperplastic polyps showed MSI-L. There was no statistically significant difference in MSI-H or MSI-L occurrence among the subtypes of polyps.

Discussion

In this study, serrated adenomas were significantly more likely to have allelic imbalance or LOH of 18q, and were significantly less likely to experience allelic imbalance of 5q than other adenomas. Progressive accumulation of inactivated tumor suppressor genes has been consistently identified in colorectal cancer, involving the *APC* gene at 5q as an early event, a chromosome 18q allele at the *DPC4/SMAD4* locus as a progression event, and the *p53* gene as the adenoma-to-carcinoma event (16). However, all colon cancers do not always follow these multistep sequence paradigms. Some colon cancers

Table 1. Genetic alterations identified in 66 colonic polyps

Tumors	Mutation			Allelic imbalance												MSI-H		
	K-*ras*			2p			3p			5q			17p			18q			+	−	*P* value
	+	−	*P* value*	AI	−	*P* value	AI	−	*P* value	AI	−	*P* value	AI	−	*P* value	AI	−	*P* value			
Hyperplastic polyps	4	7		0	10		2	8		0	11		0	11		2	8		2	9	
Adenomatous polyps																					
Serrated adenomas	2	25		3	20		5	18		0	25		0	24		7	18		3	24	
Other adenomas	10	18	$P = 0.0105$	0	27	NS	3	21	NS	6	22	$P = 0.0164$	0	27	NS	2	25	$P = 0.0458$	5	23	NS
Low-grade dysplasia	7	32		3	32		6	25		3	35		0	36		7	29		4	35	
High-grade dysplasia	5	11	NS	0	15	NS	2	14	NS	3	12	NS	0	15	NS	2	14	NS	4	12	NS
Flat adenomas†	4	29		3	28		7	22		4	27		0	30		7	24		4	29	
Exophytic adenomas	8	14	$P = 0.029$	0	19	NS	1	17	NS	2	20		0	21	NS	2	19	NS	4	18	NS

NOTE: NS, not significant; AI, allelic imbalance.
*Significance level of the difference was determined using Fisher's exact test.
†Flat adenoma refers to adenomas in which the height is not greater than twice the thickness of the adjacent normal mucosa.

Table 2. Genetic alterations in the 27 serrated adenomas

Patient no.	Sex	Age	Size (mm)	Location	Grade	K-*ras* mutation	Allelic imbalance					MSI-H
							2p	3p	5q	17p	18q	
1	M	62	8	A	HGD	–	NI	–	–	NI	–	–
2	M	71	8	D	LGD	–	–	–	–	–	–	–
3	M	82	8	D	LGD	–	NI	–	–	–	AI	–
4	M	70	5	S	LGD	–	–	–	–	–	–	–
5	M	54	6	S	LGD	–	–	NI	–	NI	–	–
6	F	68	8	T	HGD	–	–	–	–	–	–	–
7	F	75	7	A	HGD	–	–	–	–	–	AI	–
8	F	72	3	D	LGD	12 Val (GTT)*	NI	NI	–	–	–	–
9	M	42	6	D	LGD	–	–	–	–	–	AI	–
10	M	68	3	S	LGD	–	–	AI	–	–	–	–
11	F	68	5	A	LGD	12 Asp (GAT)	–	–	–	–	–	–
12	M	73	4	R	LGD	–	AI	–	–	–	–	–
13	M	53	9	R	LGD	–	–	–	–	–	AI	–
14	F	75	8	D	LGD	–	NI	AI	–	–	–	–
15	M	38	8	T	LGD	–	–	–	–	–	–	–
16	M	68	5	R	HGD	–	–	–	–	–	AI	–
17	F	83	6	S	LGD	–	AI	AI	–	–	–	MSI
18	F	77	5	S	LGD	–	–	AI	–	–	–	–
19	M	55	8	D	LGD	–	AI	–	–	–	AI	–
20	M	80	5	A	HGD	–	–	–	–	–	–	–
21	M	71	6	A	HGD	–	–	–	NI	–	–	–
22	M	70	5	D	LGD	–	–	–	–	–	AI	–
23	M	70	3	T	LGD	–	–	AI	–	–	–	–
24	M	77	5	D	LGD	–	–	–	–	NI	–	–
25	F	46	7	A	LGD	–	–	–	–	–	–	–
26	M	51	4	R	LGD	–	–	–	NI	–	NI	MSI
27	F	75	4	S	LGD	–	–	NI	–	–	NI	MSI

NOTE: 12 Asp, codon 12 aspartic acid; 12 Val, codon 12 valine; (–), no mutation, no allelic imbalance, or no MSI; NI, not informative (i.e., only one allele length obtained at PCR).
Abbreviations: A, ascending colon; T, transverse colon; D, descending colon; S, sigmoid colon; R, rectum; LGD, low-grade dysplasia; HGD, high-grade dysplasia; MSI, microsatellite instability-high, with more than two microsatellite mutations.
*Mutations are shown by the number of the codon involved and the sequence of the mutated codon.

have allelic imbalance at 18q without allelic imbalance of 5q. Serrated adenomas might be the precursors of such of colon cancers. Allelic loss of the *DCC* locus on 18q was initially reported in 40% to 60% of colorectal cancers, was thought to occur at some time before malignant conversion (16). *DPC4/SMAD4*, which maps to 18q21, has been identified as a more likely candidate tumor suppressor gene frequently mutated or deleted in colon cancers (17).

The DPC4/SMAD4 protein acts as a factor required in the transforming growth factor-β–mediated signal transduction cascade. Transforming growth factor-β stimulates the production of extracellular matrix, including glycoproteins, fibronectin, and laminin from various cells (18). Inactivation of *DPC4/SMAD4* might result in the abnormal accumulation of mucin in cellular cytoplasm because of a disorder of extracellular matrix production by the aberrant transforming growth factor-β signal. One of the speculations for the serrated appearance has been the abnormal accumulation of mucin in cellular cytoplasm (19). These findings suggest that 18q21 allelic imbalance might be an important event in the morphogenesis of serrated adenomas, and inactivation of *DPC4/SMAD4* at the 18q locus might be a key genetic alteration in these lesions. Makinen et al. (20) have suggested that mucinous adenocarcinomas are more frequent (9 of 27 cases) when there is an adjacent serrated adenoma.

One group has speculated that there may be a serrated adenoma-carcinoma sequence (13, 21). Their observations suggest that some mucinous adenocarcinomas may evolve through a serrated adenoma pathway. It has been reported that hyperplastic polyps and serrated adenomas of the colorectal show a mixed differentiation pattern, expressing both

Table 3. Genetic alterations in the 11 hyperplastic polyps

Patient	Size (mm)	Location	K-*ras* mutation*	Allelic imbalance					MSI†	Frequency
				2p	3p	5q	17p	18q		
1H	2	R	12 Asp, 13 Asp	–	–	–	–	AI	–	0 of 10
2H	2	D	–	NI	AI	–	–	–	–	0 of 10
3H	2	D	–	–	–	–	–	–	MSI-L	1 of 10
4H	2	S	–	–	–	–	–	NI	–	0 of 8
5H	3	S	–	–	–	–	–	–	MSI-L	2 of 10
6H	4	A	12 Asp, 12 Ser	–	–	–	–	–	–	0 of 9
7H	2	S	–	–	AI	–	–	–	–	0 of 9
8H	2	R	12 Asp	–	–	–	–	–	MSI-L	1 of 10
9H	4	A	12 Ser	–	NI	–	–	–	–	0 of 7
10H	2	A	–	–	–	–	–	–	MSI-H	3 of 10
11H	3	S	–	–	–	–	–	AI	MSI-L	1 of 7

NOTE: A, ascending colon; D, descending colon; S, sigmoid colon; R, rectum; AI, allelic imbalance; 12 Asp, codon 12 aspartic acid; 13 Asp, codon 13 aspartic acid; 12 Ser, codon 12 serine; (–), no mutation or no allelic imbalance; NI, not informative.
*Mutations are shown with the number of the codon involved and the new amino acid expected.
†MSI-H is based on ≥40% of markers with a novel allele when compared with normal tissue. MSI-L is based on >0% but <40% of markers with a novel allele. The number of positive markers out of the total is also indicated.

gastric (MUC1 or MUC5AC) and intestinal (MUC2) mucins (12). pS2 and human gastric mucin are expressed significantly more frequently in both hyperplastic polyps and serrated adenomas than in tubular adenomas or adenocarcinomas. It has also been reported that the serrated adenoma can show some degree of gastric differentiation (22). In future studies, it may be necessary to study inactivation of *DPC4/SMAD4* and the expression of gastric mucin phenotypes in mucinous adenocarcinomas of the colon.

In this study, we found that serrated adenomas had significantly less allelic imbalance at 5q, and fewer K-*ras* mutations, which have been noted to be frequent, early events in the genesis of the adenomatous polyp. The K-*ras* gene encodes a 21 kDa guanosine triphosphatase protein ($p21^{ras}$), which mediates signaling events regulating cell proliferation, and a single mutationally activated $p21^{ras}$ protein continuously induces cell proliferation as a genetically ''dominant'' effect. Increased cell growth induced by activating K-*ras* mutations and inactivation of *APC* seems to favor an exophytic appearance of colorectal neoplasms (5).

It has been reported that *APC* mutations are relatively infrequent in serrated adenomas (11), whereas the majority of colorectal neoplasms have inactivating mutations at the APC locus (2). K-*ras* mutations and 5q allelic imbalance events do not seem to be important in the morphogenesis of serrated adenomas, which indicates a different origin of these lesions compared with other adenomas in the colon.

Hyperplastic polyps are generally regarded as nonneoplastic lesions, however, it has been reported that some of these polyps have hyperproliferative activity (23), overexpression of p53 (24), some form of genomic instability (25), and K-*ras* mutations (26). In this study, we found that hyperplastic polyps have occasional allelic imbalance events at 18q, but not 5q. Serrated adenomas and hyperplastic polyps have some similarities in their genetic mutational signatures, including frequent 18q allelic imbalance and infrequent 5q allelic imbalance. Serrated adenomas have histologic features that resemble hyperplastic polyps, such as the saw-toothed or serrated crypts. Several reports have noted the histologic and genetic similarities between hyperplastic polyps and serrated adenomas. Our findings suggest that serrated adenomas and hyperplastic polyps have more than morphologic similarities.

Allelic imbalance at 17p was not found in any of the 66 polyps. These polyps were all small (i.e., <10 mm), and removed colonoscopically. It has been reported that allelic imbalance at 17p is frequently found in early colon cancers (5). Taken together, these findings lend additional support to the conclusion that LOH at *p53* actually mediates the adenoma to carcinoma transition (15).

In summary, serrated adenomas are significantly more likely to have an LOH event on 18q and are significantly less to experience allelic imbalance at 5q, or have K-*ras* mutations, compared with other adenomatous polyps in the colon. Serrated adenomas may evolve through a different genetic pathway than other types of adenomas in the colon.

Acknowledgments

The authors gratefully acknowledge Katsumi Miyai, Department of Pathology at the University of California, San Diego, for critical histologic consultation.

References

1. Bos JL, Fearon ER, Hamilton SR, et al. Prevalence of ras gene mutations in human colorectal cancers. Nature 1987;327:293–7.
2. Powell SM, Zilz N, Beazer-Barclay Y, et al. APC mutations occur early during colorectal tumorigenesis. Nature 1992;359:235–7.
3. Baker SJ, Preisinger AC, Jessup JM, et al. p53 gene mutations occur in combination with 17p allelic deletions as late events in colorectal tumorigenesis. Cancer Res 1990;50:7717–22.
4. Carethers JM, Hawn MT, Greenson JK, Hitchcock CL, Boland CR. Prognostic significance of allelic lost at chromosome 18q21 for stage II colorectal cancer. Gastroenterology 1998;114:1188–95.
5. Yashiro M, Carethers JM, Laghi L, et al. Genetic pathways in the evolution of morphologically distinct colorectal neoplasms. Cancer Res 2001;61:2676–83.
6. Wynter CV, Walsh MD, Higuchi T, Leggett BA, Young J, Jass JR. Methylation patterns define two types of hyperplastic polyp associated with colorectal cancer. Gut 2004;53:573–80.
7. Goel A, Arnold CN, Niedzwiecki D, et al. Characterization of sporadic colon cancer by patterns of genomic instability. Cancer Res 2003;63:1608–14.
8. Rubio CA, Kato Y, Hirota T, Muto T. Histologic classification of endoscopically removed flat colorectal polyps: a multicentric study. Jpn J Cancer Res 1996;87:849–55.
9. Urbanski SJ, Kossakowska AE, Marcon N, Bruce WR. Mixed hyperplastic adenomatous polyps–an underdiagnosed entity. Report of a case of adenocarcinoma arising within a mixed hyperplastic adenomatous polyp. Am J Surg Pathol 1984;8:551–6.
10. Longacre TA, Fenoglio-Preiser CM. Mixed hyperplastic adenomatous polyps/serrated adenomas. A distinct form of colorectal neoplasia. Am J Surg Pathol 1990;14:524–37.
11. Dehari R. Infrequent APC mutations in serrated adenoma. Tohoku J Exp Med 2001;193:181–6.
12. Jass JR. Serrated adenoma and colorectal cancer. J Pathol 1999;187:499–502.
13. Jass JR, Whitehall VL, Young J, Leggett BA. Emerging concepts in colorectal neoplasia. Gastroenterology 2002;123:862–76.
14. Boland CR, Thibodeau SN, Hamilton SR, et al. A National Cancer Institute Workshop on Microsatellite Instability for Cancer Detection and Familial Predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res 1998;58:5248–57.
15. Boland CR, Sato J, Appelman HD, Bresalier RS, Feinberg AP. Microallelotyping defines the sequence and tempo of allelic losses at tumour suppressor gene loci during colorectal cancer progression. Nat Med 1995;1:902–9.
16. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell 1990;61:759–67.
17. Hahn SA, Schutte M, Hoque AT, et al. DPC4, a candidate tumor suppressor gene at human chromosome 18q21.1. Science 1996;271:350–3.
18. Huang S, Chakrabarty S. Regulation of fibronectin and laminin receptor expression, fibronectin and laminin secretion in human colon cancer cells by transforming growth factor-β1. Int J Cancer 1994;57:742–6.
19. Jass JR, Filipe MI, Abbas S, Falcon CA, Wilson Y, Lovell D. A morphologic and histochemical study of metaplastic polyps of the colorectum. Cancer 1984;53:510–5.
20. Makinen MJ, George SM, Jernvall P, Makela J, Vihko P, Karttunen TJ. Colorectal carcinoma associated with serrated adenoma—prevalence, histological features, and prognosis. J Pathol 2001;193:286–94.
21. Leggett BA, Devereaux B, Biden K, Searle J, Young J, Jass J. Hyperplastic polyposis: association with colorectal cancer. Am J Surg Pathol 2001;25:177–84.
22. Yao T, Kouzuki T, Kajiwara M, Matsui N, Oya M, Tsuneyoshi M. 'Serrated' adenoma of the colorectum, with reference to its gastric differentiation and its malignant potential. J Pathol 1999;187:511–7.
23. Risio M, Arrigoni A, Pennazio M, Agostinucci A, Spandre M, Rossini FP. Mucosal cell proliferation in patients with hyperplastic colorectal polyps. Scand J Gastroenterol 1995;30:344–8.
24. Torlakovic E, Snover DC. Serrated adenomatous polyposis in humans. Gastroenterology 1996;110:748–55.
25. Hawkins NJ, Gorman P, Tomlinson IP, Bullpitt P, Ward RL. Colorectal carcinomas arising in the hyperplastic polyposis syndrome progress through the chromosomal instability pathway. Am J Pathol 2000;157:385–92.
26. Ajioka Y, Watanabe H, Jass JR, Yokota Y, Kobayashi M, Nishikura K. Infrequent K-ras codon 12 mutation in serrated adenomas of human colorectum. Gut 1998;42:680–4.

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