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BRAF Mutations in Aberrant Crypt Foci and Hyperplastic Polyposis

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Patients with hyperplastic polyposis have multiple hyperplastic polyps (HPs) and increased risk of colorectal carcinomas. Aberrant crypt foci (ACF) are postulated to be the earliest precursor lesions in colorectal carcinogenesis. We evaluated *BRAF* mutations by DNA sequencing in 53 ACF from patients with sporadic colorectal carcinomas and familial adenomatous polyposis, in 18 sporadic HPs from patients with resected colorectal cancer, and in 70 HPs, 4 serrated adenomas, 3 admixed hyperplastic-adenomatous polyps, 10 tubular adenomas, and 6 carcinomas from 17 patients with multiple/large HPs and/or hyperplastic polyposis. *BRAF* mutation status was compared with clinicopathological features and other genetic alterations by marginal logistic regression. *BRAF* mutation was present in only 2% of ACF and 6% of sporadic HPs. In contrast, *BRAF* mutation was present in 43% of HPs ($P = 0.01$ versus sporadic HPs), 75% of serrated adenomas, 33% of admixed hyperplastic-adenomatous polyps, 30% of tubular adenomas, and 33% of carcinomas from patients with multiple/large HPs and/or hyperplastic polyposis. *BRAF* mutation status in patients with multiple/large HPs and/or hyperplastic polyposis correlated with HPs from the same patient (odds ratio, 5.8; $P = 0.0002$) but associated with younger age (odds ratio, 0.83; $P = 0.006$ compared to older age), with a large HP (odds ratio, 22.5; $P = 0.01$ compared with patients with multiple HPs), with location of HPs in the right colon (odds ratio, 3.0; $P = 0.03$), and with methylation of the *p16* gene and the MINT31 locus [odds ratio, 12.2 ($P = 0.0001$) and 4.4 ($P = 0.02$), respectively]. Our study shows that *BRAF* mutation status is heterogeneous among patients with multiple/large HPs and/or hyperplastic polyposis, suggesting differences in pathogenesis of HPs that indicate subsets within this phenotype. ***(Am J Pathol 2005, 166:1069–1075)***

Colorectal cancer is the second most common cause of cancer deaths in the United States. Most colorectal cancers develop from adenomatous polyps, and morphological and genetic progression in an adenoma-adenocarcinoma sequence and in hereditary colorectal cancer syndromes are well described.[1–3] Aberrant crypt foci (ACF) in colorectal mucosa are the earliest known morphological precursor to colorectal cancer.[4–10] A role for ACF in colorectal carcinogenesis is supported by the presence of dysplasia in some ACF,[4,5,10] and by the presence in some ACF of genetic and epigenetic alterations that are present in colorectal carcinomas, such as alterations in the *adenomatous polyposis coli* (*APC*) tumor suppressor gene, *KRAS* proto-oncogene mutations, microsatellite instability (MSI), and methylation of *p16* gene and other CpG islands.[4–10] The histopathology of human ACF is variable but can be subclassified into dysplastic, heteroplastic (nondysplastic), and mixed types.[10] Dysplastic ACF are more common in patients with familial adenomatous polyposis (FAP), which is because of germline mutation of the *APC* gene, than in patients with sporadic colorectal neoplasia.

Sporadic HPs are usually present in the left colon, small in size, and considered to be benign in nature. However, adenocarcinoma arising in the setting of colorectal hyperplastic polyps (HPs) or serrated adenomas (SAs, polyps with serrated architecture and dysplasia)[11] especially in patients with hyperplastic polyposis have been described.[12–16] In addition, an alternative pathway of colorectal carcinogenesis with a hyperplastic polyp-serrated adenoma-adenocarcinoma sequence has been recently proposed.[17–19]

Patients with hyperplastic polyposis, characterized phenotypically by the presence of numerous HPs and/or

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large HPs, have increased risk of colorectal cancer.[15,16,20–27] It has been proposed that a majority of sporadic HPs from the right colon and HPs from patients with hyperplastic polyposis are morphologically distinct.[28] Previous studies have shown that genetic and epigenetic alterations frequent in colorectal carcinoma are present in sporadic HPs, and in HPs, SAs, admixed hyperplastic-adenomatous polyps (AHAP, polyps with admixed hyperplastic and adenomatous foci),[11] tubular adenomas, and carcinomas of patients with hyperplastic polyposis, these alterations include *KRAS* mutations, chromosome 1p loss, MSI, CpG island methylation of *p16* gene and other loci, and CpG island methylator phenotype (CIMP) with concordant methylation of CpG islands.[4,15,16,29–33]

The RAS-RAF-MEK (mitogen-activated protein/extracellular signal-regulated kinase kinase)-ERK (extracellular signal-regulated kinase)-MAP (mitogen-activated protein) kinase pathway mediates cellular responses to growth signals. *BRAF* mutations have been found in a variety of human cancers including colorectal carcinomas and melanomas.[34–39] Mutations in *BRAF* occur in two regions of the BRAF kinase domain, ie, the activation segment that protects the substrate binding site, and less commonly, the G loop that mediates binding of ATP.[40] *BRAF* mutations have also been reported in sporadic HPs and in SAs, including a few from patients with hyperplastic polyposis.[41–43] In this study, we evaluated *BRAF* mutations in ACF from patients with FAP and sporadic colorectal cancers, in sporadic HPs, and in HPs, SAs, AHAPs, tubular adenomas, and colorectal carcinomas from the patients with multiple/large HPs and/or hyperplastic polyposis. We compared the *BRAF* mutation status with polyp and patient characteristics, including correlation among multiple HPs from the same patient.

Materials and Methods

Characteristics of Patients and Specimens

All patients had given informed consent for the collection of specimens according to institutional guidelines. ACF were isolated from the grossly normal mucosa in 10 colectomy specimens from patients with sporadic colorectal cancers and from the nonpolypoid mucosa in two colectomy specimens from FAP patients with numerous polyps but no cancer. These ACF have been characterized previously.[10] Thirty ACF were from patients with sporadic colorectal cancers and 23 ACF from FAP patients. The ACF were classified as dysplastic, heteroplastic, or mixed (features of both dysplastic and heteroplastic ACF).[10]

Eighteen sporadic HPs from 15 patients undergoing resection of colorectal cancer at The University of Texas MD Anderson Cancer Center, Houston, TX, and the patients and specimens from patients with multiple/large HPs and/or hyperplastic polyposis have been reported previously (Figure 1).[16,31] The patients were classified into three groups based on the number and size of HPs: large HPs (patients with HP greater than 1 cm), hyperplastic polyposis (patients with more than 20 HPs), and multiple HPs (patients with 5 to 10 HPs), as described previously.[16] Predominance of HPs in the right colon and predominance of HPs in the left colorectum were defined by the location of the majority of HPs in the right colon or in the left colon and rectum, respectively.[31] We evaluated 70 HPs, 4 SAs, 3 AHAPs, 10 tubular adenomas, and 6 carcinomas from 17 patients with multiple/large HPs and/or hyperplastic polyposis.

Sequencing of BRAF Gene

Exons 11 and 15 of the *BRAF* gene were amplified and sequenced as previously described.[35] Exons 11 and 15 were amplified by genomic polymerase chain reaction using intronic primers and a commercial DNA sequencing kit according to the manufacturer's instructions (BigDye Terminator version 1.1 cycle sequencing kit; Applied Biosystems, Foster City, CA). The polymerase chain reaction products were analyzed with an Applied Biosystems 3730 automated sequencer using forward and reverse primers. All mutations were confirmed by an independent polymerase chain reaction amplification and sequencing. All *BRAF* mutations identified were a missense mutation at codon 599, exon 15 replacing GTG (valine) to GAG (glutamic acid). No mutations were identified in exon 11 or other codons of exon 15. Germline mutations were excluded by sequencing nonlesional DNA from these patients.

KRAS Mutations, Loss of Heterozygosity of Chromosome 1p, MSI-High, CIMP Status

KRAS mutation status of ACF, and *KRAS* mutations, loss of heterozygosity of chromosome 1p, MSI and CIMP status of sporadic HPs, and of HPs, SAs, AHAPs, tubular adenomas, and carcinomas from patients with multiple/large HPS and/or hyperplastic polyposis have been reported previously.[10,16,31] MSI-high was defined by presence of allelic shift in comparison with control DNA in at least 30% of evaluated markers. Methylation was assessed at the *p16* gene and loci methylated in tumor (MINT): MINT1, MINT2, and MINT31. MINT1 is an island associated with a cDNA transcript of unknown function. MINT2 corresponds to a CpG island that is in the 5′ region of a cDNA with an open reading frame that has no protein homology. MINT31 is 2 kb upstream of the *CACNAIG*, a T-type calcium channel gene (J.P. Issa, unpublished data). HPs, SAs, adenomas, and carcinomas were classified as CIMP-high if two or more (50%) of the *p16* gene or MINT loci were methylated, CIMP-low if one (25%) marker was methylated, and CIMP-negative if no marker was methylated.

Statistical Analysis

Patients with more than one HP were represented multiple times in this data set. To model correctly the correlation among polyps coming from the same patient as well as simultaneously partition out the effects of the various

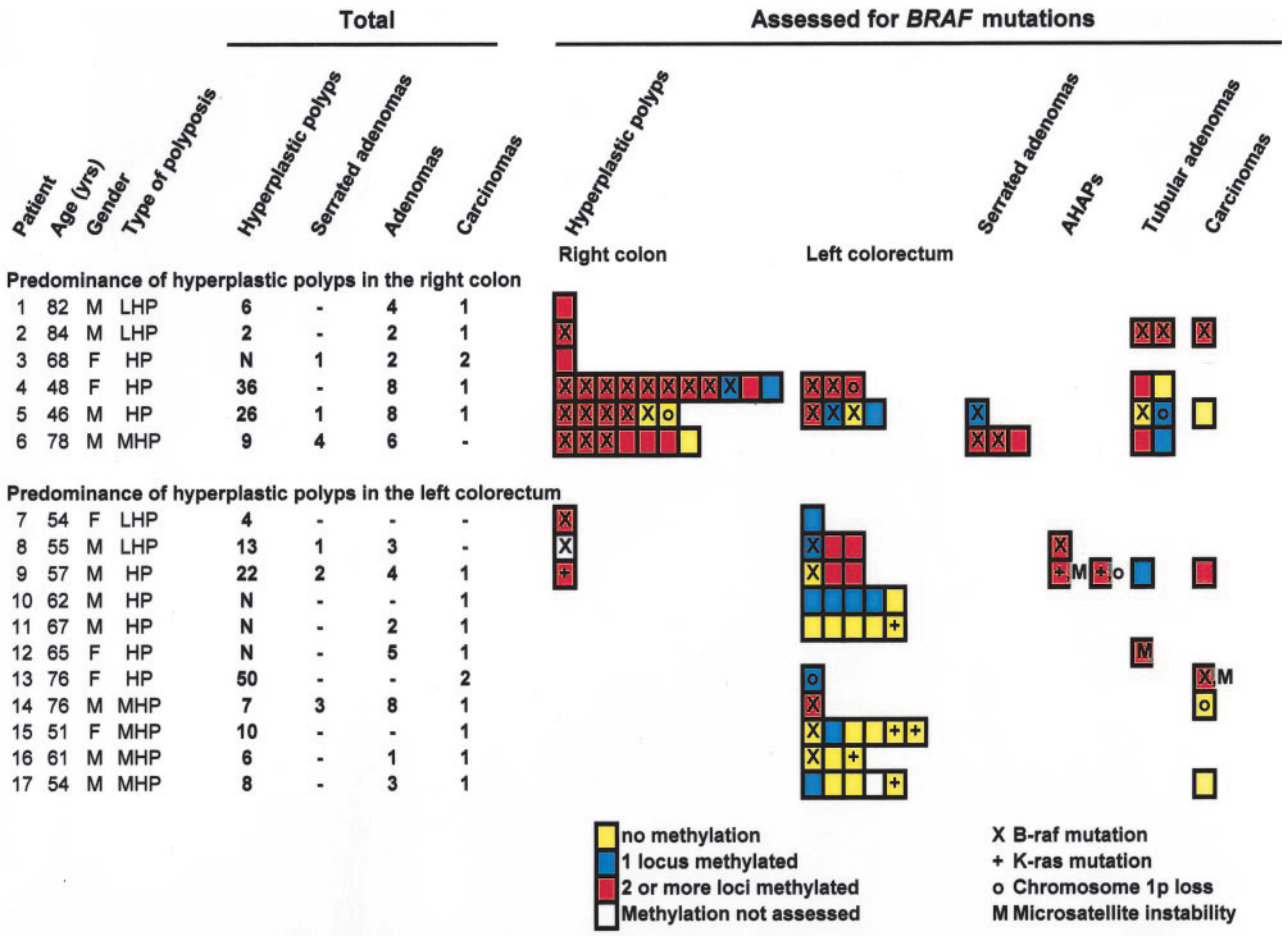

Figure 1. Clinicopathological features of patients, *BRAF* mutation status, other genetic alterations, and CIMP status of HPs, SAs, AHAPs, tubular adenomas, and carcinomas from patients with large/multiple HPs, and/or hyperplastic polyposis.

factors considered, marginal logistic regression models for correlated binary data[44] were used to assess associations between *BRAF* mutations and the various polyp and patient characteristics. These associations were tested for association with *BRAF* mutations and were represented as odds ratios, in which an odds ratio of greater than one suggests positive correlation of *BRAF* mutations with patients or polyp characteristics, respectively. We used three models. The first model with no factors was used to estimate the correlation among the *BRAF* mutation status in polyps from the same patient, without adjusting for other covariates. A second model included various patient- and polyp-level factors, including the methylation status of the *p16* gene and MINT1, MINT2, and MINT31 loci as potential predictors of *BRAF* mutation status. A third model was used with CIMP status (CIMP-high versus CIMP-low and CIMP-negative) substituted in place of the methylation status of the *p16* gene and MINT1, MINT2, MINT31 loci, individually. The statistical analysis was performed using PROC GENMOD in SAS (SAS Institute, Cary, NC), using an assumption that all polyps within a patient were equally correlated. In all models, factors with *P* values less than 0.05 were considered statistically significant.

Results

ACF

Twenty-three ACF were from 2 FAP patients and 30 ACF from 10 patients with sporadic colorectal carcinomas. As previously reported,[10] 91% (21 of 23) of ACF from FAP patients were dysplastic and 9% (2 of 23) were heteroplastic. In contrast, 87% (26 of 30) of ACF from patients with sporadic colorectal cancer were heteroplastic, only 10% (3 of 10) were dysplastic, and 3% (1 of 30) were mixed. *BRAF* mutation was present in 0% (0 of 23) of ACF from FAP patients and only 3% (1 of 30) of ACF from patients with sporadic colorectal cancers (Figure 2A). In contrast, *KRAS* mutation was present in 4% (1 of 23) of ACF from FAP patients and 40% (12 of 30) of ACF from patients with sporadic colorectal cancers. *BRAF* mutation was present in a heteroplastic ACF and was the missense

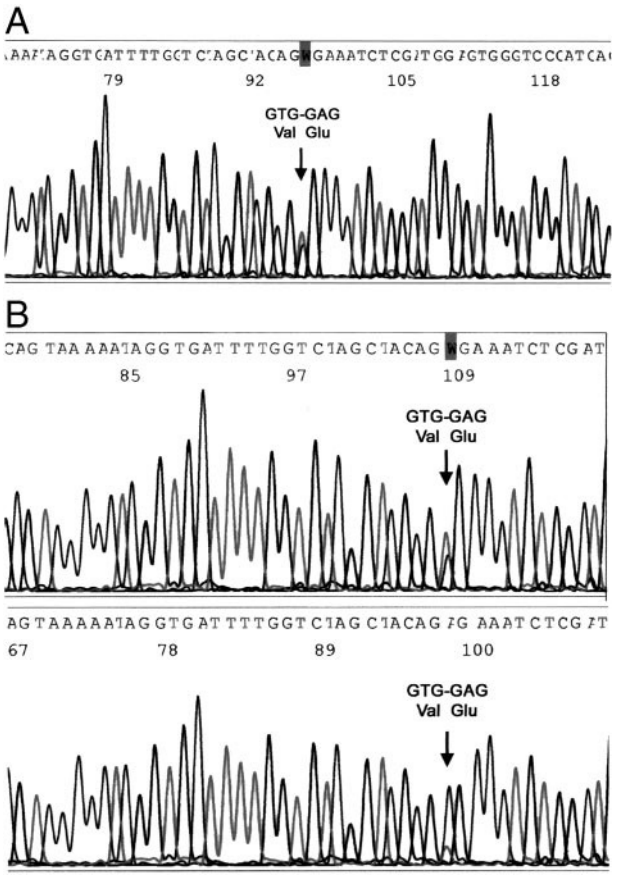

Figure 2. A: Nucleotide sequencing of exon 15 of *BRAF* gene in ACF. **B:** Nucleotide sequencing of exon 15 of *BRAF* gene in HPs. The T to A missense point mutation at codon 599 with replacement of valine with glutamic acid is indicated by **arrows**. The wild-type and mutated nucleotide and amino acid sequences are shown on **top**.

point mutation at codon 599 as described in the Materials and Methods.

Sporadic HPs

The sporadic HPs were from 12 men and 3 women, with a mean age of 64 ± 11 years (range, 48 to 80 years). The mean size of the polyp in this group was 0.3 cm (range, 0.1 to 0.7 cm). There were 3 HPs from the right colon and 15 from the left colorectum. *BRAF* mutation was present in 6% (1 of 18) of sporadic HPs. *BRAF* mutation was again the missense point mutation at codon 599 described above. No *KRAS* mutation or methylation of the *p16* gene or MINT loci were present in sporadic HPs.

Hyperplastic Polyposis

There were 11 men and 6 women with multiple/large HPs and/or hyperplastic polyposis. The mean age was 64 ± 12 years (range, 46 to 84 years). The demographic data and characteristics of each individual patient and the number of HPs, adenomas, and carcinomas in each individual are summarized in Figure 1. *BRAF* mutations in patients are summarized in Figure 1, and representative examples of sequencing are shown in Figure 2B. *BRAF* mutations were present in 43% (30 of 70) of HPs (P = 0.01 versus sporadic HPs), 75% (3 of 4) of SAs, 33% (1 of 3) of AHAPs, 30% (3 of 10) of tubular adenomas, and 33% (2 of 6) of carcinomas from patients with multiple/large HPs and/or hyperplastic polyposis. All *BRAF* mutations in HPs and other lesions from patients with multiple/large HPs and/or hyperplastic polyposis were the missense point mutation at codon 599 as described in the Materials and Methods.

We first examined if the *BRAF* mutation status was correlated within HPs from the same patient. We used a model with no factors except the correlation. We found that the correlation was statistically significant (odds ratio, 5.8; P = 0.0002; Figure 1 and Table 1). The odds ratio of 5.8 means that given the presence of a *BRAF* mutation in a polyp from a given patient, the probability of another polyp in the same patient having the *BRAF* mutation is 5.8 times greater than if the first polyp did not have the *BRAF* mutation.

We next examined associations of *BRAF* mutation status to various patient and polyp characteristics (summarized in Figure 1 and Table 1). We found that patient age, type of polyposis, polyp site, and methylation for *p16* gene and MINT31 were significant predictors for *BRAF* mutation status. Specifically, we found that HPs from older patients were less likely to have the mutation (odds ratio, 0.83; P = 0.006). This odds ratio means that there is a 17% decrease in probability of *BRAF* mutation for every year older a given subject is. *BRAF* mutations were present in 50% (4 of 8) of HPs from patients with a large HP compared to 27% (6 of 22) of HPs from patients with multiple HPs (odds ratio, 22.5, compared with patients with multiple HPs; P = 0.01), in 67% (20 of 30) of HPs from the right colon compared to 25% (10 of 40) of HPs from the left colon and rectum (odds ratio, 3.0; P = 0.03), in 80% (12 of 15) of HPs with *p16* gene methylation compared to 32% (13 of 41) without *p16* methylation (odds ratio, 12.2; P = 0.0001), and in 58% (22 of 38) of HPs with methylation at MINT31 locus compared to 23% (7 of 31) without methylation at MINT31 (odds ratio, 4.4; P = 0.02). The correlation was statistically significant in this model (odds ratio, 3.6; P = 0.02), indicating that there was still evidence of correlation even after adjusting for the factors present in this model. The other factors were not independently associated with *BRAF* mutation status.

In the third model, CIMP status was substituted for the methylation statuses of the *p16* gene, and MINT1, MINT2, and MINT31 in model two (Table 1). HPs with CIMP-high were slightly more likely to have *BRAF* mutations, but this was not significant after adjusting for other factors. Other genetic alterations in HPs and other lesions have been previously reported.[16] *KRAS* mutations were present in 9% (6 of 70) of HPs and 67% (2 of 3) of AHAPs but in none of 4 SAs, 10 tubular adenomas, or 6 carcinomas (Figure 1). Chromosome 1p loss was present in 4% (3 of 70) of HPs, 33% (1 of 3) of AHAPs, 10% (1 of 10) of tubular adenoma, and 17% (1 of 6) of carcinomas, but in none of four SAs. MSI was present in 33% (1 of 30) of AHAPs, 10% (1 of 10) of tubular adenomas, and 17% (1 of 6) of carcinomas, but in none of four SAs. Except for

Table 1. Patient and Polyp Characteristics in Relation to *BRAF* Mutation Status of Hyperplastic Polyps in Patients with Multiple/Large HPs and/or Hyperplastic Polyposis, Odds Ratio and 95% Confidence Intervals from GEE Marginal Regression Models

Model and factors	*BRAF* mutations		Odds ratio (95% confidence intervals)	χ^2	*P*
	Present % (fraction)	Absent % (fraction)			
One					
Correlation			5.8 (1.6, 2.3)	14.5	0.0002
Two					
Patient characteristics					
Correlation			3.6 (1.3, 1.7)	10.1	0.02
Age (continuous, years)			0.83 (0.7, 1.1)	0.6	0.006
Patients with large hyperplastic polyps	50 (4/8)	50 (4/8)	22.5 (2.0, 3.5)	259.9	0.01
Patients with hyperplastic polyposis	50 (20/40)	50 (20/40)	1.4 (0.2, 2.9)	10.9	0.8
Patients with multiple hyperplastic polyps	27 (6/22)	73 (18/22)	1.0		
Patients with serrated adenoma or AHAP†	56 (15/27)	44 (12/27)	4.1 (0.5, 2.9)	34.6	0.2
Patients without serrated adenoma or AHAP	35 (15/43)	65 (28/43)	1.0		
Hyperplastic polyp characteristics					
Size (continuous, mean ± SD, mm)	4.4 ± 4.2	3.2 ± 1.5	1.2 (0.7, 1.3)	1.9	0.5
Site					
Right	67 (20/30)	33 (10/30)	3.0 (1.1, 1.7)	8.0	0.03
Left	25 (10/40)	75 (30/40)	1.00		
p16 methylation					
Present	80 (12/15)	20 (3/15)	12.2 (1.4, 6.1)	24.3	0.0001
Absent	32 (13/41)	68 (28/41)	1.00		
Unassessed	36 (5/14)	64 (9/14)			
MINT1 methylation					
Present	75 (12/16)	25 (4/16)	0.8 (0.1, 3.2)	7.4	0.8
Absent	30 (15/50)	70 (35/50)	1.00		
Unassessed	75 (3/4)	25 (1/4)			
MINT2 methylation					
Present	59 (22/37)	41 (15/37)	0.9 (0.1, 2.9)	7.5	0.9
Absent	18 (5/28)	82 (23/28)	1.00		
Unassessed	60 (3/5)	40 (2/5)			
MIINT31 methylation					
Present	58 (22/38)	42 (16/38)	4.4 (1.2, 1.9)	15.8	0.02
Absent	23 (7/31)	77 (24/31)	1.00		
Unassessed	100 (1/1)	0 (0/1)			
Three*					
CIMP status					
High	64 (21/33)	36 (12/33)	1.7 (0.2, 2.8)	12.7	0.6
Low or absent	23 (8/35)	77 (27/35)	1.00		
Unassessed	50 (1/2)	50 (1/2)			

*In this model CIMP status was substituted for methylation statuses of *p16* gene, and MINT1, MINT2, MINT31.
†Admixed hyperplastic-adenomatous polyp, AHAP.

one carcinoma with *BRAF* mutation and MSI, all other genetic alterations were inversely related to *BRAF* mutations in all other lesions.

Discussion

We studied *BRAF* mutations in ACF from patients with FAP and sporadic colorectal cancers, sporadic HPs, and HPs and other colorectal lesions from patients with multiple/large HPs and/or hyperplastic polyposis. We found *BRAF* mutation status was correlated in HPs from patients with multiple/large HPs, or hyperplastic polyposis. *BRAF* mutations have been reported in sporadic colorectal carcinomas,[34–40,42] adenomas,[35] and HPs.[35,41–43] However, *BRAF* mutations are uncommon in sporadic microsatellite-stable colorectal carcinomas but are more frequent in MSI-high carcinomas[36–39] because of methylation of *hMLH1* gene.[36,39] All *BRAF* mutations in our study were T to A missense point mutation at codon 599 with replacement of valine with glutamic acid. No mutation of exon 11 or other codons of exon 15 were found. In contrast, previous studies have reported *BRAF* mutations involving other codons, although infrequently, in colorectal cancers and other colorectal lesions including HPs.[34,35,37,39,41]

The reported frequency of *BRAF* mutations in HPs and other serrated lesions is variable. In our study *BRAF* mutations were present in 43% of HPs, 75% of SAs, and 33% of AHAPs from patients with multiple/large HPs and/or hyperplastic polyposis, but were infrequent in sporadic HPs that were predominately from the left colon and rectum. These results are corroborated by another study that reported *BRAF* mutations in 13% of sporadic serrated polyps (including HPs, SAs, and AHAP) but in 88% of serrated polyps from four patients with hyperplastic polyposis.[42] However, two previous studies reported higher frequencies of *BRAF* mutations in serrated polyps from sporadic patients.[41,43] In one study BRAF mutations

were present in 36% of HPs, 100% of SAs, and 20% of AHAP,[41] and in the other 70% of HPs and 60% of SAs.[43] These differences could be because of the methodology used for the detection of *BRAF* mutations, or to heterogeneity and selection bias of the study populations among our and previous studies.

In our study, *BRAF* mutation status was correlated among multiple HPs from the same patient and was more frequent in younger patients, patients with a large HP and right-sided polyps. This is corroborated by reports of increased frequency of *BRAF* mutations in right-sided serrated polyps[42] and right-sided colonic carcinomas.[36,39] We and others have previously reported more frequent CIMP-high in right-sided HPs,[31,45] and differences in topographic expression of $p21^{Waf1/Cip1}$ cyclin-dependent kinase inhibitor and Ki-67 proliferation marker in right- and left-sided HPs from these patients.[16] In addition, the HPs from the right colon are morphologically different from the HPs in the left colorectum.[28] These data suggest that right-sided HPs are morphologically and genetically different from the left-sided HPs in patients with sporadic HPs and in those with multiple/large HPs and/or hyperplastic polyposis.

The genetic alterations in sporadic HPs differ from the alterations in HPs from patients with multiple/large HPs, and/or hyperplastic polyposis. Sporadic HPs have more frequent *KRAS* mutations but less frequent *BRAF* mutations[41–43] or loss of chromosome 1p,[29,30,46] and lack CpG island methylation.[31,42,45] In contrast, the present study and previous studies have reported that the HPs from patients with multiple/large HPs and/or hyperplastic polyposis have frequent *BRAF* mutations and CpG island methylation, but infrequent *KRAS* mutations or loss of chromosome 1p.[16,31,42,45] Furthermore, *KRAS* mutation or loss of chromosome 1p was predominantly present in HPs from patients with predominance of HPs in left colorectum,[16,31] a set of patients that lacked *BRAF* mutations or CIMP-high HPs.

The data from our present study and previous studies[42,45] suggest that HPs and other lesions from patients with multiple/large HPs and/or hyperplastic polyposis have *BRAF* mutations and CIMP-high but lack MSI. In contrast, sporadic colon carcinomas with *BRAF* mutations frequently have MSI.[36–39] In our study, *BRAF* mutations were more frequent in tubular adenomas in patients with multiple/large HPs and/or hyperplastic polyposis compared to sporadic adenomas.[35] These data provide additional evidence that progression of colorectal carcinogenesis in patients with multiple/large HPs and/or hyperplastic polyposis is distinct from sporadic colorectal carcinomas. In some patients with multiple/large HPs and/or hyperplastic polyposis, HPs and other lesions have CIMP-high and *BRAF* mutations similar to sporadic CIMP-high colorectal carcinomas but lack MSI-high. Other patients have HPs and other lesions that lack *BRAF* mutation and CpG island methylation, as documented by four patients with loss of chromosome 1p or *KRAS* mutations in the majority of their HPs.[16,31]

In our study *BRAF* mutations were infrequent in ACF from patients with sporadic colorectal cancers and FAP. Dysplastic ACF are characterized by abnormal epithelial proliferation in the upper aspects of the crypts, lack of *KRAS* mutations and methylation, and presence of *APC* mutations in dysplastic ACF from FAP patients but not patients with sporadic colorectal cancers.[8–10] The lack of *BRAF* mutations in dysplastic ACF or heteroplastic ACF from FAP patients is not surprising and is further corroborated by infrequent *BRAF* mutations in sporadic adenomas or adenomas from patients with FAP.[35] In contrast, heteroplastic ACF are characterized by lack of dysplasia, have proliferation mainly in the lower aspects of the crypts, have frequent *KRAS* mutations and methylation, and lack *APC* mutations.[4,8–10] Heteroplastic and mixed ACF resemble HPs and SAs histopathologically, respectively. These data suggest that either heteroplastic ACF are not precursors of HPs, SAs, and colorectal cancers with *BRAF* mutations, or *BRAF* mutation is a late event in a hyperplastic polyp-serrated adenoma-carcinoma sequence. Alternatively, these findings may be because of selection bias in our study with ACF from sporadic colorectal cancers and FAP, a patient-population that lacks *BRAF* mutations.

Recent studies have suggested a hyperplastic polyp-serrated adenoma-carcinoma pathway in colorectal carcinogenesis.[17–19] Right-sided sporadic colon carcinomas often have CpG island methylation and *BRAF* mutations. In this study we show that some patients with multiple/large HPs and/or hyperplastic polyposis have these molecular characteristics in multiple colonic lesions including HPs. As a consequence, it appears that subsets of patients whose lesions have different pathogenesis have similar phenotypes. Molecular characteristics are needed to identify those subsets.

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