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Original contribution

Targeted mutational analysis of inflammatory bowel disease–associated colorectal cancers☆,☆☆

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Summary Inflammatory bowel disease–associated colorectal carcinomas (IBD-CRCs) develop in a background of chronic inflammation, and thus, the molecular landscape of these tumors likely differs from that of sporadic colorectal cancer. To add to emerging data on molecular alterations present in these tumors, we analyzed our institution's cohort of IBD-CRCs. CRCs resected from patients with IBD underwent molecular analysis via a 50-gene hot-spot solid tumor panel (OncoScreen ST2.0). In-house sporadic CRCs and The Cancer Genome Atlas project data were used for comparison. Fifty-five IBD-CRCs from 48 patients were successfully analyzed. Mutations in *TP53* were most common and were present in 69% of IBD-CRCs; a similar percentage of *TP53* mutations was detected in sporadic colorectal carcinomas (70%). *APC* and *KRAS* mutations were significantly less common in IBD-CRCs than in sporadic CRCs (15% versus 53%, $P < .001$ and 20% versus 38%, $P = .02$, respectively). Additionally, the potentially targetable *IDH1* R132 mutation was present in 7% of IBD-CRCs but only 1% of sporadic CRCs and The Cancer Genome Atlas CRCs; alterations in other genes with potential targeted therapies were very rare. In conclusion, IBD-CRCs exhibit molecular differences when compared to sporadic CRCs, suggesting different pathways of carcinogenesis, although certain alterations are common to both types of tumors. *IDH1* mutations are present in a subset of IBD-CRCs, which may expand therapeutic options in the future.

1. Introduction

Early genomic studies of colorectal carcinoma (CRC) identified loss of *APC* function as a crucial first step in the development of these tumors, after which alterations in additional driver genes occur and allow tumor cells to invade surrounding tissues [1]. Although alterations in as few as 3 such driver genes are still considered sufficient for the development of

Abbreviations IBD-CRC, inflammatory bowel disease–associated colorectal carcinoma; TCGA, The Cancer Genome Atlas; MMR, mismatch repair

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CRC, sequencing of these tumors has identified a number of recurrently altered genes in CRC, most of which appear to play key roles in a limited number of cell signaling pathways [2]. However, the molecular landscape of subsets of CRCs, including those arising in a background of inflammatory bowel disease (IBD), has only recently been explored [3,4].

IBD-associated CRCs (IBD-CRCs) develop in a background of chronic inflammation that is thought to result in widespread oxidative stress–induced DNA damage [1,5]. The presence of a large field effect is supported by the frequent occurrence of multifocal tumors in IBD patients [6]. IBD-CRCs also reportedly exhibit characteristic histologic features, including a high frequency of mucinous and signet ring cell differentiation [7]. Such pathologic differences suggest that the mutational landscape of IBD-CRCs may also differ from that of sporadic CRCs.

With the growing availability of next-generation sequencing, exploring this landscape has become increasingly feasible, and the results of 2 studies comparing mutations in cancer-related genes between IBD-CRCs and sporadic CRCs were recently published. These studies revealed a lower frequency of *APC* alterations and a higher frequency of *TP53* alterations in IBD-CRCs compared to sporadic CRCs, although the frequency of *TP53* alterations was quite variable, ranging from 63% to 89% [3,4]. Additionally, *IDH1* was identified as a recurrently altered gene in IBD-CRCs, with mutations in this gene more often described in patients with Crohn disease (CD) than in those with ulcerative colitis (UC) [3,8].

Given the limited number of patients analyzed in the previous studies, we sought to add to emerging data by performing targeted mutational analysis on the University of Chicago's cohort of IBD-CRCs. We compared the results to sequencing data from non–IBD-associated CRCs within our institution as well as to data from The Cancer Genome Atlas' (TCGA) CRC study. Using these data and immunohistochemical (IHC) staining, we also evaluated these tumors for genetic alterations and protein expression that may indicate the presence of potential therapeutic targets in these tumors. Finally, we compared the genomic alterations occurring in CD and UC patients and correlated our molecular findings with a variety of other clinicopathological features.

2. Materials and methods

2.1. Case selection

Cases of CRC arising in IBD patients with resections performed between 2000 and 2015 were identified from the University of Chicago pathology archive. Hematoxylin and eosin–stained slides from all cases were reviewed by a gastrointestinal pathologist, and a representative tumor-containing slide was selected for molecular testing. Clinicopathological data were collected from pathology reports, electronic medical records, and the institutional cancer registry. This study was approved by the University of Chicago's Institutional Review Board (IRB16-0042).

2.2. Immunohistochemical analysis

Cases for which IHC for mismatch repair (MMR) proteins had not been previously performed underwent immunohistochemical staining with antibodies against MSH6 (clone EPR3945, 1:200 dilution, Abcam, Cambridge, MA) and PMS2 (clone EPR3945, 1:50 dilution, Abcam, Cambridge, MA); if loss of 1 of these proteins was detected, the appropriate partner stain (MSH2 [clone FE11, 1:50 dilution, Dako, Carpinteria, CA] or MLH1 [ES05, 1:50 dilution, Dako, Carpinteria, CA], respectively) was performed.

2.3. Genomic analysis

DNA was prepared from slides cut from formalin-fixed, paraffin-embedded (FFPE) tissue blocks of resection specimens using the QIAamp DNA FFPE Tissue Kit (Qiagen, Valencia, CA) per the manufacturer's instructions. Cases with sufficient DNA underwent OncoScreen ST2.0 testing. OncoScreen ST2.0 is a 50-gene hot-spot solid tumor panel that uses the Ion Ampliseq Cancer Hotspot Panel V2 primer set (Thermo Fisher Scientific, Waltham, MA) for amplification of 207 hot-spot targeted amplicons across 50 genes. The assay detects mutations above 10% mean allele frequency and has been extensively validated for performance on FFPE tissue [9]. The test contains amplicons for hot-spot locations of the following genes: *ABL1*, *AKT1*, *ALK*, *APC*, *ATM*, *BRAF*, *CDH1*, *CDKN2A*, *CSF1R*, *CTNNB1*, *EGFR*, *ERBB2*, *ERBB4*, *EZH2*, *FBXW7*, *FGFR1*, *FGFR2*, *FGFR3*, *FLT3*, *GNA11*, *GNAQ*, *GNAS*, *HNF1A*, *HRAS*, *IDH1*, *IDH2*, *JAK2*, *JAK3*, *KDR*, *KIT*, *KRAS*, *MET*, *MLH1*, *MPL*, *NOTCH1*, *NPM1*, *NRAS*, *PDGFRA*, *PIK3CA*, *PTEN*, *PTPN11*, *RB1*, *RET*, *SMAD4*, *SMARCB1*, *SMO*, *SRC*, *STK11*, *TP53,* and *VHL.*

After sequencing, data were analyzed using a custom-developed in-house clinical pipeline, and all variants were annotated using Alamut Batch 1.4.4 software (http://www.interactive-biosoftware.com/), followed by further filtering to detect and annotate potential somatic variants using the 1000 Genomes Project, Exome Sequencing Project, Exome Aggregation Consortium, Catalog of Somatic Mutations in Cancer, and cBioPortal for Cancer Genomics. Variants deemed pathogenic, likely pathogenic, and of uncertain significance were included in the analysis, whereas those deemed benign were excluded.

OncoScreen ST2.0 results from 91 non–IBD-associated CRC samples (non–IBD-CRCs) previously tested at the University of Chicago were used for comparison.

2.4. Statistical analysis

Descriptive statistics for categorical variables were conducted by χ^2 statistics; 2-tailed Pearson significance (P) values

are reported, except for 2 × 2 tables with any cell frequency less than 5, for which Fisher exact statistics are reported. Student *t* tests were conducted for continuous variables. Statistical significance was defined as a $P < .05$.

3. Results

3.1. Patient characteristics

We identified 72 IBD-CRCs resected during the study period. OncoScreen ST2.0 testing was successful in 55 tumors from 48 patients. Of these cases, 35 tumors were from 30 patients with UC (2 patients with 2 synchronous tumors and 1 patient with 4 synchronous tumors), 18 tumors were from 16 patients with CD (1 patient with 3 synchronous tumors), and 2 tumors were from 2 patients with indeterminate colitis. Clinicopathological features of the cases are provided in Table 1. The mean patient age at diagnosis was 48 years (standard deviation 12 years), and three quarters of the patients were male. Two patients had a history of primary sclerosing cholangitis, both of whom had UC. On average, patients had been diagnosed with IBD 21 years before they developed CRC (standard deviation 11 years). Most patients had pancolitis, and approximately 40% had a documented history of dysplasia prior to the current resection. The tumors were almost evenly distributed throughout the right and left colon and rectum. Approximately a third of cases were classified as mucinous or signet ring cell carcinomas, and half of all cases were high grade. A pathologic stage of T3 was most common, and lymph node metastases were present in nearly half of the cases. Although the mean time from IBD diagnosis to CRC was slightly shorter in CD cases than in UC cases (18 ± 10 years versus 26 ± 13 years, $P = .04$), there were no other significant differences in clinicopathological features between CD and UC cases (Table 1).

3.2. Mutations in IBD-CRCs

A co-mutation plot detailing the frequencies of alterations, the genes altered in each case, and the type of alteration present (missense mutation, nonsense mutation, splice site alteration, or frameshift insertion/deletion) is provided in the Figure. Genes altered in at least 5% of cases are listed in Table 2, along with the frequencies of these mutations in non–IBD-CRCs and TCGA CRCs. Mutations in *TP53* were most common and were detected in 69% (38/55) of IBD-CRCs; a similar percentage of *TP53* mutations was detected in non–IBD-CRCs (70%, 64/91), but TCGA CRCs had significantly fewer *TP53* mutations than IBD-CRCs (54%, 121/224, $P = .04$). In contrast, both *APC* and *KRAS* mutations were present in a minority of IBD-CRCs (15% or 8/55 and 20% or 11/44, respectively) and were significantly more common in non–IBD-CRCs (53% or 48/91 and 38% or 35/91, respectively) and TCGA CRCs (75% or 168/224 and 42% or 94/224, respectively). Additionally, the potentially targetable *IDH1* R132 mutation was seen in 7% (4/55) of IBD-CRCs but was present in only 1% of non–IBD-CRCs and TCGA CRCs. *PIK3CA, SMAD4,* and

Table 1 Clinicopathological features

	All patients [a]	UC	CD	UC *vs* CD *P*
Age, y (mean ± SD)	48 ± 12 (n = 48)	48 ± 12 (n = 30)	47 ± 11 (n = 16)	.80
Years of IBD at CRC (mean ± SD)	21 ± 11 (n = 47)	26 ± 13 (n = 29)	18 ± 10 (n = 16)	.04
Male sex	75% (36/48)	80% (24/30)	75% (12/16)	.70
Pancolitis	86% (38/44)	89% (25/28)	86% (12/14)	1.00
Documented history of dysplasia	40% (17/43)	39% (11/28)	38% (5/13)	1.00
Tumor location				.18
Right	41% (22/54)	37% (13/35)	47% (8/17)	
Left	33% (18/54)	43% (15/35)	18% (3/17)	
Rectum	26% (14/54)	20% (7/35)	35% (6/17)	
Tumor size, cm (mean ± SD)	4.4 ± 2.7 (n = 43)	4.0 ± 2.0 (n = 29)	5.4 ± 4.0 (n = 14)	.15
Mucinous or signet ring carcinoma	35% (19/55)	26% (9/35)	44% (8/18)	.17
High grade	51% (27/53)	50% (17/34)	47% (8/17)	.84
pT stage				.42
1	14% (7/51)	10% (3/31)	22% (4/18)	
2	20% (10/51)	23% (7/31)	17% (3/18)	
3	41% (21/51)	45% (14/31)	28% (5/18)	
4	25% (13/51)	23% (7/31)	33% (6/18)	
pN stage				.12
0	52% (28/54)	47% (16/34)	67% (12/18)	
1	28% (15/54)	38% (13/34)	11% (2/18)	
2	20% (11/54)	15% (5/34)	22% (4/18)	

[a] Includes 2 patients with indeterminate colitis.

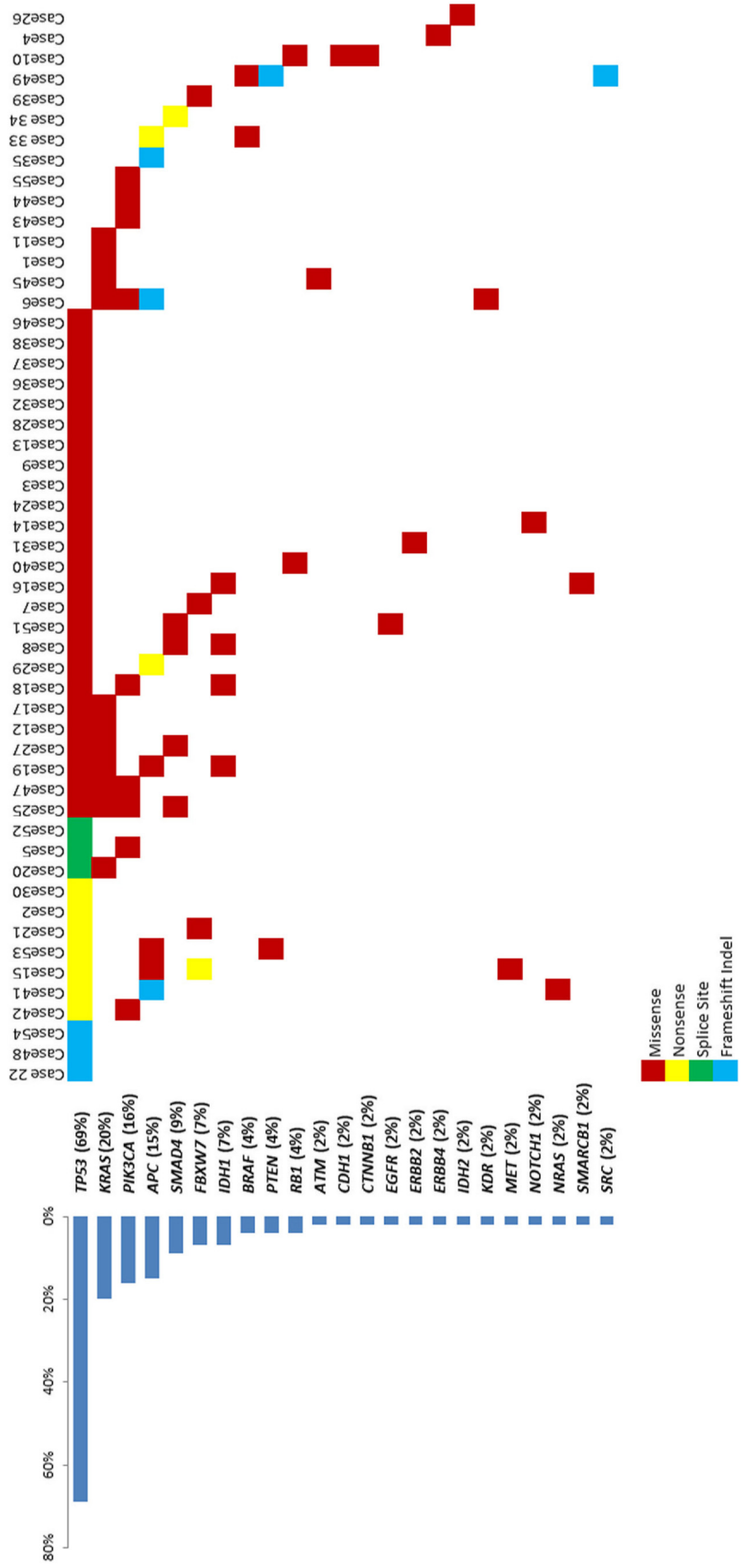

Figure Co-mutation plot summarizing genomic alterations in IBD-CRCs.

Table 2 Genes altered in >5% of IBD-CRCs and comparison with non-IBD in-house and TCGA CRCs

Gene	IBD-CRCs (n = 55)	Non–IBD-CRCs (n = 91)	TCGA (n = 224)	IBD *vs* non–IBD-CRCs *P*	IBD *vs* TCGA *P*
TP53	69% (38)	70% (64)	54% (121)	.89	.04
KRAS	20% (11)	38% (35)	42% (94)	.02	.003
PIK3CA	16% (9)	25% (23)	20% (45)	.21	.53
APC	15% (8)	53% (48)	75% (168)	<.0001	<.0001
SMAD4	9% (5)	10% (9)	12% (26)	.86	.60
IDH1	7% (4)	1% (1)	1% (3)	.07	.03
FBXW7	7% (4)	8% (7)	17% (37)	1.00	.09

FBXW7 were also mutated in >5% of IBD-CRCs. *FBXW7* mutations were over twice as common in TCGA CRCs than in either of the other groups, but the difference did not reach statistical significance. The frequencies of *PIK3CA* and *SMAD4* mutations were similar between groups. Further details on sequence variants in IBD-CRCs can be found in Supplementary Table 1.

3.3. Targeted therapy and IBD-CRCs

Alterations in genes that are targets of FDA-approved CRC therapies or CRC therapies in phase III clinical trials were very rare in IBD-CRCs (Table 3) [10]. *BRAF* mutations were detected in 2/55 cases (4%), whereas 10/91 (11%) of non–IBD-CRCs and 20/224 (9%) of TCGA CRCs had *BRAF* mutations. One IBD-CRC (2%) had an *EGFR* mutation; no *FGFR1, FGFR2, FGFR3, KIT,* and *FLT3* alterations were identified in the IBD-CRCs. Alterations in these potentially targetable genes in non–IBD-CRCs and TCGA CRCs ranged from 1% to 11% of cases (Table 3).

3.4. Immunohistochemical analysis of IBD-associated colorectal carcinomas

Of the 55 IBD-CRCs, only 3 cases (5%) demonstrated loss of 1 or more MMR proteins by IHC. One case demonstrated isolated MSH6 loss and was found to have mutations in *KRAS*, *APC*, *PIK3CA*, and *KDR*. Two cases demonstrated loss of MLH1 and PMS2; one of these cases had mutations in *BRAF, PTEN*, *SRC,* and *ATK1*, whereas the other had a *PIK3CA* mutation.

3.5. Genomic comparison of CD- and UC-associated colorectal carcinomas

Several differences were detected in the frequencies of mutations in CD- and UC-associated CRCs (Table 4). Mutations in *IDH1* were seen in 3 cases of CD and 1 case of indeterminate colitis, but this mutation was not detected in any of the UC-associated CRCs. In contrast, 4 UC cases demonstration *FBXW7* mutations, but mutations in this gene were not found in any of the CD cases. Although mutations in *APC* were uncommon in both subsets of IBD-CRCs, they were more common in CD than UC (22% or 4/18 versus 11% or 4/35), although the difference was not statistically significant (P = .42). Similarly, there was a nonsignificant trend toward increased *PIK3CA* mutations in UC cases (23% or 8/35 versus 6% or 1/18; P = .14).

3.6. Correlation of mutations with clinicopathological features

We also examined the relationship of the most frequently detected mutations in IBD-CRCs (*TP53*, *KRAS*, *PIK3CA*, and *APC*) to clinicopathological features. There was no significant association between any of these mutations and age, sex, tumor location, mucinous or signet ring cell histology, lymphovascular invasion, or presence of lymph node metastases. Additionally, there was no significant association between the presence of these molecular alterations and the T stage of the tumors. There was a trend toward increased *PIK3CA* mutations with increasing age, but this association did not reach statistical significance (P = .09). Similarly, there was a trend

Table 3 Genes with potential targeted therapy [a] in colorectal carcinoma

Gene	Therapy	IBD-CRCs (n = 55)	Non–IBD-CRCs (n = 91)	TCGA CRCs (n = 224)
BRAF	Binimetinib	4% (2)	11% (10)	9% (21)
EGFR	Cetuximab, panitumumab	2% (1)	1% (1)	4% (10)
FGFR1, 2, 3	Nintedanib	0% (0)	0% (0)	3% (7)
FLT3	Nintedanib	0% (0)	0% (0)	2% (4)
KIT	Anlotinib	0% (0)	0% (0)	3% (6)

[a] FDA-approved or in phase III clinical trial.

Table 4 Alterations in colorectal carcinomas arising in UC versus CD

Gene	UC (n = 35)	CD (n = 18)	*P*
TP53	63% (22)	78% (14)	.36
KRAS	17% (6)	28% (5)	.48
PIK3CA	23% (8)	6% (1)	.14
APC	11% (4)	22% (4)	.42
SMAD4	9% (3)	6% (1)	1.00
IDH1	0% (0)	17% (3)	.04
FBXW7	11% (4)	0% (0)	.29

toward increased mucinous and signet ring cell histologic features in cases with *KRAS* mutations, which was not statistically significant ($P = .10$). Additionally, although *IDH1* was not one of the most frequently altered genes in IBD-CRCs, 3 of the 4 tumors with *IDH1* mutations exhibited mucinous and/or signet ring cell features.

4. Discussion

Our next-generation sequencing analysis of tumor hot-spot genes in IBD-CRCs provides further evidence that the molecular alterations present in these tumors differ from those of sporadic CRCs. As in previous studies, we found *TP53* to be the most commonly mutated gene in IBD-CRCs, whereas the frequency of *APC* and *KRAS* mutations was significantly lower than in sporadic CRCs. These findings support the theory that IBD-CRCs do not arise through the *APC*-inactivated adenoma pathway of sporadic CRCs but instead arise through alternate pathways, including foci of dysplasia harboring *TP53* mutations [5,11]. In addition, mutations in the *IDH1* R132 hot-spot, the target of selective IDH1 inhibitors currently in early stages of investigation in solid tumors, was seen in a significantly higher frequency of IBD-CRCs compared to sporadic CRCs.

Although our findings overall were comparable to those seen in previous studies, there were a few key differences. *TP53* alterations occurred in 69% of our IBD-CRCs (38/55), which is similar to the frequency reported by Robles et al (63%, 20/32) and higher than the frequency seen in sporadic CRCs by TCGA (54%, 121/224) [2,4]. However, Yaeger et al detected *TP53* alterations in a much higher percentage of IBD-CRCs: 89% (42/47) [3]. The frequency of *KRAS* alterations in our IBD-CRCs (20%, 11/55) was also similar to that of Robles et al (20%, 6/30) but was again much lower than the frequency of these alterations reported by Yaeger et al (40%, 19/47) [3,4]. Differences in methodology, particularly our use of a hot-spot–focused technique, may explain the lower frequency of alterations detected in our cases compared to the study of Yaeger et al. In their study, the entire coding sequence of the genes was analyzed, and the authors noted that *TP53* mutations in their IBD-CRCs were present outside of the gene's hot-spots, supporting this theory. Additionally, the presence of intratumoral heterogeneity, which has been reported to occur in some CRCs with *KRAS* mutations, could also have contributed to the lower frequency of *KRAS* mutations in our cases [12]. Finally, our in-house control group of non–IBD-CRCs was noted to have a higher frequency of *TP53* alterations (70%, 64/91) compared to TCGA CRCs (54%, 121/224) [2]. This difference could be related to the small number of cases in our in-house control group compared to the TCGA CRC group. Given these findings, although it does appear that IBD-CRCs have a high frequency of *TP53* mutations, the frequency may not be significantly different from that of sporadic CRCs.

In addition to our next-generation sequencing analysis of IBD-CRCs, we also assessed the MMR protein status of these cases by IHC. Approximately 15% of sporadic CRCs are reported to have mismatch repair deficiency, and 10% of TCGA CRCs (23 cases) demonstrated high levels of microsatellite instability [2,13]; several large studies have reported similar rates of microsatellite instability in IBD-CRCs (9%-15%) [14,15]. However, only 5% (3/55) of our IBD-CRCs demonstrated MMR protein loss. The reason for this low rate of MMR deficiency in our study is unclear, but it may again be related to our relatively small sample size. Within our MMR-deficient IBD-CRCs, 2 cases demonstrated loss of MLH1 and PMS2, 1 of which was found to have an underlying *BRAF* mutation. The third case exhibited isolated MSH6 loss, which suggests that a germline mutation in the *MSH6* gene was the source of MMR deficiency in this case. Although extremely rare, IBD has been described in patients with Lynch syndrome, including Lynch syndrome due to *MSH6* mutations, and patients with both of these conditions have a high risk of developing CRC at a young age [16].

We also noted molecular differences between CD- and UC-associated CRCs in our study, some of which have been previously described. *APC* alterations were twice as common in CD-associated CRCs compared to UC-associated CRCs (22% or 4/18 versus 11% or 4/35), although unlike in previous studies, this difference did not reach statistical significance ($P = .42$) [3]. We also saw an increased prevalence of *PIK3CA* mutations in UC-associated CRCs compared to CD-associated CRCs (23% or 8/35 versus 6% or 1/18), although this association also did not reach statistical significance ($P = .14$). Alterations in *FBXW7*, although rare, were only detected in UC-associated CRCs, which to our knowledge is a finding that has not been previously described. As mentioned earlier, *IDH1* mutations were present in 3 CD-associated CRCs and 1 CRC in a patient with indeterminate colitis, but this alteration was not seen in any UC-associated CRCs, which is similar to the findings described by Yaeger et al [3]. However, rare cases of UC-associated CRCs with *IDH1* mutations have been reported, so *IDH1* mutations may not be entirely specific for CD-associated CRCs [8]. Interestingly, 3 of 4 of the *IDH1*-mutated tumors in our study exhibited mucinous and/or signet ring cell histologic features, which is an association that has not been reported in previous studies; in fact, Hartman et al specify that none of the 3 IBD-CRCs harboring *IDH1* mutations in their study exhibited such histologic

features [8]. Given the small number of cases with *IDH1* mutations in both studies, the relationship between *IDH1* and tumor histology remains unclear. Although the above findings suggest that the type of IBD present may affect the molecular landscape of IBD-CRCs, larger studies or a meta-analysis would be necessary to further evaluate the significance of our findings. Other than these findings, we did not detect any significant associations between clinicopathological features and molecular alterations.

Finally, our analysis of hot-spot mutations in IBD-CRCs also provides insight into the potential use of targeted therapies in these tumors. Unfortunately, our results suggest that targets of currently available therapies are rare in IBD-CRCs, although mutations in *IDH1*, an investigational target in other malignancies, do appear to occur in a subset of IBD-CRCs, so a trial involving such tumors may be warranted.

There are several limitations to our study, many of which are related to our use of a hot-spot gene panel. Restricting our analysis to previously identified tumor hot-spots may have led to underestimation of the frequency of mutations in each gene. Additionally, we did not analyze copy number variation in our study, and previous studies suggest that this mechanism plays an important role in IBD-CRC tumorigenesis. For instance, Yaeger et al identified *MYC* amplification resulting in Wnt/B-catenin pathway inactivation in a sizeable subset of IBD-CRCs, which could in part explain the low frequency of *APC* alterations detected in these tumors [3,4]. Other limitations of this study include its inclusion of cases from only a single institution and its retrospective analysis.

In summary, our study adds to the growing data on the molecular landscape of IBD-associated CRCs and supports the theory that most of these tumors arise through a different pathway from sporadic CRCs, although certain alterations, such as *TP53* mutations, are common to both sets of tumors. Additionally, we confirmed that mutations in the potentially targetable *IDH1* gene are present in some IBD-CRCs, which may expand therapeutic options for these patients in the future. Further studies that include analysis of non-neoplastic tissue and precursor lesions are necessary to determine the precise sequence of molecular events leading to tumorigenesis in IBD.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humpath.2019.04.013.

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