

# World Journal of *Clinical Oncology*

*World J Clin Oncol* 2022 October 24; 13(10): 762-865



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**RESPONSIBLE EDITORS FOR THIS ISSUE**

Production Editor: Xiang-Di Zhang; Production Department Director: Xu Guo; Editorial Office Director: Yu-Jie Ma.

**NAME OF JOURNAL**

*World Journal of Clinical Oncology*

**ISSN**

ISSN 2218-4333 (online)

**LAUNCH DATE**

November 10, 2010

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Hiten RH Patel, Stephen Safe, Jian-Hua Mao, Ken H Young

**EDITORIAL BOARD MEMBERS**

<https://www.wjgnet.com/2218-4333/editorialboard.htm>

**PUBLICATION DATE**

October 24, 2022

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<https://www.wjgnet.com/bpg/gerinfo/242>

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<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

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## Retrospective Cohort Study

# Somatic mutations in FAT cadherin family members constitute an underrecognized subtype of colorectal adenocarcinoma with unique clinicopathologic features

Liang-Li Wang, Wei Zheng, Xiu-Li Liu, Feng Yin

**Specialty type:** Oncology**Provenance and peer review:**

Invited article; Externally peer reviewed.

**Peer-review model:** Single blind**Peer-review report's scientific quality classification**

Grade A (Excellent): A

Grade B (Very good): B

Grade C (Good): C

Grade D (Fair): 0

Grade E (Poor): 0

**P-Reviewer:** Aktekin A, Turkey; Osera S, Japan; Yang Z, China**Received:** July 26, 2022**Peer-review started:** July 26, 2022**First decision:** August 18, 2022**Revised:** August 25, 2022**Accepted:** September 15, 2022**Article in press:** September 15, 2022**Published online:** October 24, 2022**Liang-Li Wang, Feng Yin**, Department of Pathology and Anatomical Sciences, University of Missouri School of Medicine, Columbia, MO 65212, United States**Wei Zheng**, Department of Pathology, Emory University School of Medicine, Atlanta, GA 30322, United States**Xiu-Li Liu**, Department of Pathology and Immunology, Washington University, St. Louis, MO 63110, United States**Corresponding author:** Feng Yin, MD, PhD, Assistant Professor, Department of Pathology and Anatomical Sciences, University of Missouri School of Medicine, One Hospital Drive, Columbia, MO 65212, United States. [fengyin@health.missouri.edu](mailto:fengyin@health.missouri.edu)

## Abstract

### BACKGROUND

The FAT cadherin family members (FAT1, FAT2, FAT3 and FAT4) are conserved tumor suppressors that are recurrently mutated in several types of human cancers, including colorectal carcinoma (CRC).

### AIM

To characterize the clinicopathologic features of CRC patients with somatic mutations in FAT cadherin family members.

### METHODS

We analyzed 526 CRC cases from The Cancer Genome Atlas PanCancer Atlas dataset. CRC samples were subclassified into 2 groups based on the presence or absence of somatic mutations in *FAT1*, *FAT2*, *FAT3* and *FAT4*. Individual clinicopathological data were collected after digital slide review. Statistical analysis was performed using *t* tests and chi-square tests.

### RESULTS

This CRC study cohort had frequent mutations in the *FAT1* (10.5%), *FAT2* (11.2%), *FAT3* (15.4%) and *FAT4* (23.4%) genes. Two hundred CRC patients (38.0%) harbored somatic mutations in one or more of the *FAT* family genes and were grouped into the FAT mutated CRC subtype. The FAT-mutated CRC subtype was more commonly located on the right side of the colon (51.0%) than in the rest of

the cohort (30.1%,  $P < 0.001$ ). It showed favorable clinicopathologic features, including a lower rate of positive lymph nodes (pN1-2: 33.5% *vs* 46.4%,  $P = 0.005$ ), a lower rate of metastasis to another site or organ (pM1: 7.5% *vs* 16.3%,  $P = 0.006$ ), and a trend toward an early tumor stage (pT1-2: 25.0% *vs* 18.7%,  $P = 0.093$ ). *FAT* somatic mutations were significantly enriched in microsatellite instability CRC (28.0% *vs* 2.1%,  $P < 0.001$ ). However, *FAT* somatic mutations in microsatellite stable CRC demonstrated similar clinicopathologic behaviors, as well as a trend of a better disease-free survival rate (hazard ratio = 0.539; 95% confidence interval: 0.301-0.967; log-rank  $P = 0.073$ ).

### CONCLUSION

*FAT* cadherin family genes are frequently mutated in CRC, and their mutation profile defines a subtype of CRC with favorable clinicopathologic characteristics.

**Key Words:** *FAT* cadherin family genes; Colorectal adenocarcinoma; Clinicopathologic features; Prognosis; The Cancer Genome Atlas

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**Core Tip:** Colorectal carcinoma (CRC) is the third most common cancer and the second leading cause of cancer-related deaths worldwide. In this study, we aimed to characterize the clinicopathologic features of CRC patients with somatic mutations in *FAT* cadherin family members. CRC cases have frequent mutations in *FAT* family genes. The *FAT*-mutated CRC subtype is more commonly located on the right side of the colon and shows favorable clinicopathologic features, including a lower rate of positive lymph nodes and a lower rate of metastasis to another site or organ, suggesting that the *FAT* somatic mutation is a potentially independent prognostic factor in CRC.

**Citation:** Wang LL, Zheng W, Liu XL, Yin F. Somatic mutations in *FAT* cadherin family members constitute an underrecognized subtype of colorectal adenocarcinoma with unique clinicopathologic features. *World J Clin Oncol* 2022; 13(10): 779-788

**URL:** <https://www.wjgnet.com/2218-4333/full/v13/i10/779.htm>

**DOI:** <https://dx.doi.org/10.5306/wjco.v13.i10.779>

## INTRODUCTION

Colorectal carcinoma (CRC) is the third most common cancer and the second leading cause of cancer-related deaths worldwide, with more than 1.9 million new cases and 935000 deaths in 2020[1]. Except for a few CRC cases (5%-10%) with inherited gene mutations, most CRC cases occur sporadically and exhibit chromosomal instability that leads to changes in chromosome numbers and structure, featuring aneuploidy, loss of heterozygosity, subkaryotypic amplification, and chromosomal rearrangement. Along with karyotypic abnormalities, mutations in specific tumor suppressor genes and oncogenes, such as the adenomatous polyposis (*APC*) gene, tumor protein p53 (*TP53*) and *KRAS* proto-oncogene GTPase, also contribute to CRC tumorigenesis. Notably, mutation of the *APC* gene, which leads to the activation of Wnt/ $\beta$ -catenin signaling, is an essential and early event in the development of CRC[2,3].

Despite the well-defined genetic and epigenetic alterations in CRC initiation and progression, recent studies have shown that the Hippo pathway may interact with Wnt/ $\beta$ -catenin signaling and play a crucial role in controlling intestinal stem cell proliferation and CRC development[4]. The Hippo pathway is an emerging tumor suppressor pathway. As a proposed upstream component of the Hippo pathway, the atypical cadherin *FAT* acts as a receptor to activate the Hippo pathway[5], and its mutation appears to be a recurrent event in human cancers in association with dysregulation of the Hippo pathway[6].

The human *FAT* cadherin gene family comprises the *FAT1*, *FAT2*, *FAT3* and *FAT4* genes[7-10]. The encoded proteins *FAT1-4* are human homologs of *Drosophila* *FAT*, of which *FAT1* and *FAT4* have been reported to be involved in the regulation of planar cell polarity[11] and tumor suppression[12,13]. *FAT1* also promotes actin-mediated cell migration[14,15] and plays a role in epithelial mesenchymal transition [16]. Somatic mutations of *FAT* family genes have been detected in different human cancers, including squamous cell carcinoma of the head and neck (*FAT1*, *FAT2* and *FAT4*)[17-20], breast cancer (*FAT1*)[21], melanomas (*FAT4*)[22], leukemia (*FAT1*)[23,24], hepatocellular cancer (*FAT1*, *FAT4*)[25,26], esophageal squamous cell carcinoma (*FAT1*)[27-29], pancreatic cancer (*FAT1*, *FAT3* and *FAT4*)[30,31], and gastric cancer (*FAT4*)[32,33]. Alterations in *FAT* family genes are associated with tumorigenesis and prognosis. For instance, upregulation of the *FAT1* gene is associated with poor prognosis and early relapse in acute

lymphoblastic leukemia patients[24] and invasive progression of ductal carcinoma *in situ*[21], while loss of *FAT4* is associated with invasiveness in gastric cancer[34]. Until now, the role of *FAT* family genes in CRC tumorigenesis has not been well studied. In this study, we characterized the clinicopathologic features of *FAT* family gene mutations in CRC patients.

## MATERIALS AND METHODS

### Study design

In total, 526 CRC cases were selected from The Cancer Genome Atlas (TCGA) PanCancer Atlas dataset. cBioPortal (<https://www.cbioportal.org/>) was used to download whole-exome somatic mutation data and clinical information. There are certain sample inclusion criteria for the TCGA PanCancer Atlas on colorectal adenocarcinoma. The biospecimens were collected from newly diagnosed colorectal adenocarcinoma patients undergoing surgical resection, regardless of histologic grade or tumor stage. The patients had not received prior chemoradiation therapy. The histological sections contained an average of 60% tumor cells with less than 20% necrosis[35].

In the TCGA PanCancer Atlas dataset, the somatic mutation profiles of *FAT1*, *FAT2*, *FAT3* and *FAT4* were analyzed for each tumor. Furthermore, the CRC cases were categorized into two groups based on their mutational status on *FAT* family genes: The cases with mutant *FAT1-4* and the cases with wild-type *FAT1-4*. Standard demographic and clinicopathological data were retrieved for each patient, including age, sex, tumor location, pT stage, pN stage, pM stage, differentiation grade, tumor type, lymphovascular invasion, month of disease-free survival (DFS) and overall survival (OS).

### Statistical analyses

Demographic and clinicopathological details were stratified according to *FAT1-4* mutation. Quantitative and qualitative variables were expressed as the means  $\pm$  SD and the frequencies. Comparisons between the groups were analyzed with *t* tests and chi-square tests. DFS and OS were analyzed using the Kaplan-Meier method, and the log-rank test was used to assess differences. The figure was prepared using GraphPad Prism 9 software (GraphPad Software, San Diego, California, United States). *P* values less than 0.05 were considered statistically significant.

## RESULTS

### Patient characteristics

The study included 526 patients with CRC from TCGA PanCancer Atlas Dataset. The mean age of the patients was 65.8 years (SD 13.0 years; range: 31-90 years). Based on the available clinicodemographic information, two hundred fifty-two patients were female, and two hundred seventy-two patients were male. Of them, 254 (48.3%) patients had left-sided colon cancer, and 197 (37.5%) patients had right-sided colon cancer. The majority (72.4%) of the CRCs were moderately differentiated adenocarcinomas. The detailed demographics, histopathologic stage and features are summarized in [Table 1](#).

### Somatic mutations of *FAT* family genes in CRC

Among the 526 CRC cases, 200 (38.0%) patients harbored one or more somatic mutations of the *FAT* cadherin family genes, including mutations in the *FAT1* (10.5%), *FAT2* (11.2%), *FAT3* (15.4%), and *FAT4* (23.4%) genes. The somatic mutation types of the *FAT* family genes include missense mutation, nonsense mutation, splicing mutation, frameshift deletion, frameshift insertion and in-frame deletion, with missense mutation being the most common somatic mutation type ([Table 2](#)). Interestingly, these somatic mutations were significantly enriched in the extracellular cadherin domain (*FAT1*, 49.0%; *FAT2*, 63.4%; *FAT3*, 40.1%; *FAT4*, 57.8%) ([Table 2](#)).

Based on the presence or absence of somatic mutations in *FAT1-4* genes, these cases were subclassified into 2 groups in our study. The clinicopathologic features of these 2 subtypes are summarized in [Table 3](#). In the *FAT*-mutated CRC subtype, the median patient age was 66.5 years (range: 33-90 years), and 102 (51.0%) patients were male. Compared with the rest of the cohort, the *FAT*-mutated CRC subtype was more commonly located on the right side of the colon (51.0% *vs* 30.1%, *P* < 0.001) and more commonly associated with favorable histopathologic features, including lower pathological nodal stage (pN0: 66.5% *vs* 52.8%, *P* = 0.005), lower rate of metastasis to another site or organ (pM1: 7.5% *vs* 16.3%, *P* = 0.006), and a trend of lower pathological tumor stage (pT1-2: 25.0% *vs* 18.7%, *P* = 0.093).

### *FAT* somatic mutations are enriched in microsatellite-unstable CRC

Human *FAT* family genes encode large atypical cadherin proteins with a large number of cadherin repeats. Given the overlapping features found in the *FAT*-mutated CRC subtype and microsatellite-unstable (MSI) CRC (right sided with favorable clinicopathological features), we further explored the association between *FAT* mutations and MSI. Interestingly, *FAT* somatic mutations were significantly

**Table 1** Clinicodemographics and histologic features in 526 patients with colorectal adenocarcinoma (PanCancer Atlas)

Feature	Level	Number	MSS number
Age (yr), mean $\pm$ SD		65.8 $\pm$ 13.0	65.4 $\pm$ 12.7
Gender	Female	252 (47.9%)	218 (47.1%)
	Male	272 (51.7%)	243 (52.5%)
	Unknown	2 (0.4%)	2 (0.4%)
Histopathologic differentiation	Well	19 (3.6%)	18 (3.9%)
	Moderate	381 (72.4%)	351 (75.8%)
	Poor	114 (21.7%)	83 (17.9%)
	Unknown	12 (2.3%)	11 (2.4%)
Tumor location	Left	254 (48.3%)	248 (53.6%)
	Right	197 (37.5%)	149 (32.2%)
	Left and right	3 (0.6%)	3 (6.5%)
	Unknown	72 (13.7%)	63 (13.6%)
Tumor staging (pT)	T1	18 (3.4%)	17 (3.7%)
	T2	94 (17.9%)	83 (17.9%)
	T3	355 (67.5%)	310 (67.0%)
	T4	57 (10.8%)	52 (11.2%)
	TX	2 (0.4%)	2 (0.4%)
Nodal staging (pN)	N0	305 (58.0%)	255 (55.1%)
	N1	128 (24.3%)	120 (25.9%)
	N2	90 (17.1%)	85 (18.4%)
	NX	3 (0.6%)	3 (6.5%)
Metastasis (pM)	M0	388 (73.8%)	338 (73.0%)
	M1	68 (12.9%)	66 (14.3%)
	MX	70 (13.3%)	59 (12.7%)
Lymphovascular invasion	Present	178 (33.8%)	157 (33.9%)
	Absent	230 (43.7%)	202 (43.6%)
	Unknown	118 (22.4%)	104 (22.5%)
Ethnicity	Caucasian	273 (51.9%)	236 (51.0%)
	African-American	60 (11.4%)	51 (11.0%)
	Asian	12 (2.3%)	11 (2.4%)
	Unknown	181 (34.4%)	165 (35.6%)
Subtype	CIN	328 (62.4%)	
	MSI	63 (12.0%)	
	GS	58 (11.0%)	
	POLE	10 (1.9%)	
	Unknown	57 (10.8%)	
Total		526	463

CIN: Chromosomal instability; MSI: Microsatellite instability; GS: Genomically stable; POLE: Polymerase epsilon mutation; MSS: Microsatellite stable.

enriched in MSI CRC (28.0% vs 2.1%,  $P < 0.001$ ) (Table 3).

**Table 2 Genetic mutation types and numbers in *FAT* family genes in colorectal adenocarcinoma (PanCancer Atlas)**

Gene	Missense mutation	Nonsense mutation	Splicing mutation	Frame shift deletion	Frame shift insertion	Inframe deletion	Total mutation	Mutation in Cadherin domains
FAT1	85	5	2	3	2	1	98	48 (49.0%)
FAT2	90	2	3	5	1	0	101	64 (63.4%)
FAT3	124	6	0	5	2	0	137	55 (40.1%)
FAT4	198	19	0	10	4	0	230	133 (57.8%)

To control for confounding in the analysis, we focused on cases of microsatellite-stable (MSS) CRC. As shown in [Table 1](#), the MSS CRC cases showed similar clinicodemographic and histologic features as the entire cohort. We also categorized the MSS CRC cases into 2 groups based on the mutation status of *FAT* family genes. Similar to the entire cohort we described earlier, the *FAT*-mutated MSS CRC subtype was also more commonly located on the right side of the colon (39.6% *vs* 28.8%,  $P = 0.038$ ) and more commonly associated with favorable histopathologic features, such as a lower rate of metastasis to another site or organ (pM1: 9.0% *vs* 16.6%,  $P = 0.038$ ). It also showed a trend of lower pathological tumor stage (pT1-2: 26.4% *vs* 19.1%,  $P = 0.083$ ) and lower pathological nodal stage (pN0: 60.4% *vs* 52.7%,  $P = 0.079$ ) ([Table 3](#)). Therefore, even though it is enriched in MSI CRC, the *FAT* somatic mutation is a potentially independent prognostic factor in CRC.

The median DFS for CRC patients was 26.0 mo (0.5-148.0 mo), and the OS was 21.0 mo (0-148.0 mo). Consistent with the favorable pathologic features, the *FAT*-mutated MSS CRC subgroup showed a trend toward a better DFS rate [hazard ratio (HR) = 0.539; 95% confidence interval (CI): 0.301-0.967; log-rank  $P = 0.073$ ]. However, *FAT* mutation status did not show a significant impact on the OS rate (HR = 1.198; 95% CI: 0.770-1.864; log-rank  $P = 0.440$ ) ([Figure 1](#)).

## DISCUSSION

To our knowledge, this is the first study to assess the impact of somatic mutations in *FAT* family genes on clinicopathologic features, with an emphasis on prognosis in CRC patients. Our study shows that somatic mutations in *FAT* family genes are associated with favorable clinicopathologic features, including a lower rate of lymph node and distal metastasis. It also showed a trend toward a lower tumor stage with a relatively favorable DFS.

In addition to the *APC-β-catenin* pathway, which represents the most prominent signaling pathway in CRC, components of the Hippo pathway have been reported to be involved in CRC tumorigenesis[36-40] and have been proposed as prognostic factors in CRC[41-44]. As an upstream organizer and activator of the Hippo pathway[6], *FAT* family genes have emerged as an important mechanism that orchestrates epithelial development as well as human cancer initiation and progression. The *FAT* family genes (*FAT1-4*) encode atypical cadherins that contain multiple extracellular cadherin repeats, laminin G motifs and EGF-like motifs[45]. Among these, *FAT1* and *FAT4* are relatively well studied. Loss of *FAT4* expression has been reported in some primary breast cancers and breast cancer cell lines[46]. Low *FAT4* expression was also observed in gastric cancers and was associated with a poor prognosis, including high pathologic T stage, an increase in perineural invasion, high lymph node metastasis and reduced DFS[47]. Similarly, a study reported recurrent *FAT1* mutations in multiple human cancers, including glioblastoma, CRC, and head and neck cancer, and *FAT1* mutations affected patient survival by promoting Wnt signaling and tumorigenesis[48]. Our study demonstrates that somatic mutations in *FAT* family genes are frequent recurrent events in CRC and that *FAT* mutations are associated with favorable clinicopathologic features. These somatic mutations are highly enriched in the extracellular cadherin domains ([Table 2](#)). *FAT* proteins are large single transmembrane receptors characterized by 32-34 extracellular cadherin repeats. These cadherin repeats contain highly conserved binding sites for proteins, such as beta-catenin and p120-catenin, which are important for the *FAT* protein to execute its role in migration, polarity and cell adhesion by linking it to the actin cytoskeleton.

Our study also revealed the significant enrichment of *FAT*-mutated CRC (28.0%) in the MSI subgroup. However, the clinicopathologic characteristics in *FAT*-mutated MSS CRC are quite compatible with the entire *FAT*-mutated CRC cohort in our study, suggesting that MSI only partially contributes to its pathologic features and clinical outcomes. Interestingly, *FAT*-mutated MSS CRC cases showed a trend of favorable DFS but not OS. The underlying mechanisms of this discrepancy are currently unclear. Notably, DFS does not always correlate with OS in CRC, such as in the case of liver-only metastatic CRC[49].

Similar to the findings in our study, Wang *et al*[33] reported a superior prognosis in gastric adenocarcinoma with *FAT* family gene mutations. In their study, *FAT* gene mutations were significantly associated with better progression-free survival and OS, which was likely attributed to the significantly

**Table 3 Association of clinicopathologic features with *FAT* somatic mutations in colorectal adenocarcinoma (PanCancer Atlas)**

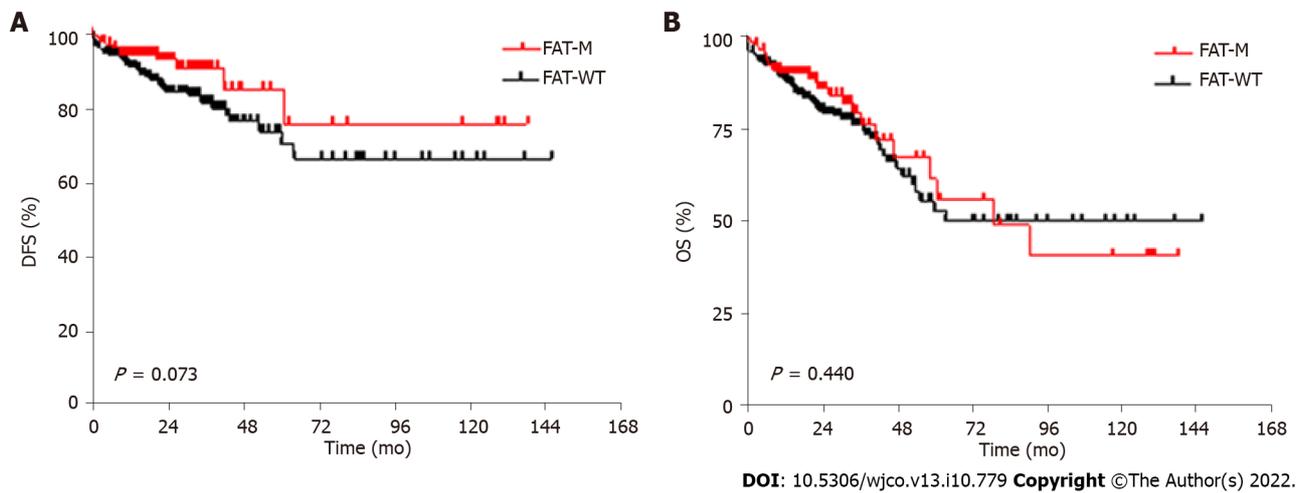
Clinicopathologic features	Mutated <i>FAT</i> genes	Wildtype <i>FAT</i> genes	<i>P</i> value	Mutated <i>FAT</i> genes (MSS)	Wildtype <i>FAT</i> genes (MSS)	<i>P</i> value
Mean age (mean ± SD)	66.5 ± 12.9	65.3 ± 13.0	0.912	65.6 ± 12.1	65.3 ± 12.9	
Sex			0.689			0.825
Female	98 (49.0%)	154 (47.2%)		67 (46.5%)	151 (47.3%)	
Male	102 (51.0%)	170 (52.1%)		77 (53.5%)	166 (52.0%)	
Location			< 0.001 <sup>a</sup>			0.038 <sup>a</sup>
Left side	65 (32.5%)	181 (55.5%)		70 (48.6%)	178 (55.8%)	
Right side	102 (51.0)	98 (30.1%)		57 (39.6%)	92 (28.8%)	
pT stage			0.093			0.083
pT1-2	50 (25.0%)	61 (18.7%)		38 (26.4%)	61 (19.1%)	
pT3-4	150 (75.0%)	263 (80.7%)		106 (73.6%)	256 (80.3%)	
pN stage			0.005 <sup>a</sup>			0.079
pN0	133 (66.5%)	172 (52.8%)		87 (60.4%)	168 (52.7%)	
pN1	44 (22.0%)	84 (25.8%)		39 (27.1%)	81 (25.4%)	
pN2	23 (11.5%)	67 (20.6%)		18 (12.5%)	67 (21.0%)	
pM stage			0.006 <sup>a</sup>			0.038 <sup>a</sup>
pM0	153 (76.5%)	235 (72.1%)		110 (76.4%)	228 (71.5%)	
pM1	15 (7.5%)	53 (16.3%)		13 (9.0%)	53 (16.6%)	
Differentiation grade			0.332			0.172
G1-2	145 (72.5%)	255 (78.2%)		117 (81.3%)	252 (79.0%)	
G3	47 (23.5%)	67 (20.6%)		20 (13.9%)	63 (19.7%)	
Subtype			< 0.001 <sup>a</sup>			
CIN	92 (46.0%)	236 (72.4%)				
MSI	56 (28.0%)	7 (2.1%)				
GS	25 (12.5%)	33 (10.1%)				
Lymphovascular invasion			0.313			0.516
Positive	61 (30.5%)	117 (35.9%)		44 (30.6%)	113 (35.4%)	
Negative	90 (45.0%)	140 (42.9%)		63 (43.8%)	139 (43.6%)	
Total	200 (38.0%)	326 (62.0%)		144 (31.1%)	319 (68.9%)	

<sup>a</sup>*P* < 0.05.

CIN: Chromosomal instability; MSI: Microsatellite instability; GS: Genomically stable; MSS: Microsatellite stable.

higher tumor mutational burden and an inflamed tumor microenvironment[33]. Whether the tumor microenvironment plays a similar role in CRC still awaits further investigation.

Our study has several limitations. First, our findings were obtained from a bioinformatics study on somatic mutation profiles through the TCGA PanCancer Atlas dataset. The protein expression levels of individual *FAT* family members were not systematically examined in the study, and the underlying molecular mechanisms related to the prognostic role of the *FAT* family in colorectal cancer need further experimental validation. Second, all the patients in the study were untreated, with no therapy response data and a short follow-up. Therefore, the evaluation of advanced-stage CRC is relatively limited. Third, we tried to address the impact of MSI status, a confounding factor, by analyzing the MSS samples. However, there are still additional potential confounding factors, such as histopathological subtypes, *TP53* mutation status, and intratumoral spatial and temporal heterogeneity. The ability of our study to address these potential confounding factors is hampered by intrinsic limitations of the TCGA database, the landmark cancer program heavily focused on cancer genomics datasets. A randomized, large-scale clinical cohort is necessary to validate our conclusion and to establish somatic mutations in *FAT* family



**Figure 1** Kaplan-Meier curves of disease-free survival and overall survival in microsatellite-stable colorectal adenocarcinoma patients without and with *FAT* family gene mutations. A: Disease-free survival; B: Overall survival. FAT-M: *FAT* mutated; FAT-WT: Wild-type *FAT*; DFS: Disease-free survival; OS: Overall survival.

genes as independent prognostic factors for CRC in future studies.

## CONCLUSION

In summary, our study shows that somatic mutations in *FAT* family genes are recurrent genetic events detected in approximately 38% of CRC cases and therefore represent an underrecognized subtype of CRC. The *FAT*-mutated CRC subtype shows unique clinicopathologic features, including a right-side location, a lower rate of positive lymph nodes, a lower rate of metastasis to another site or organ, and a trend toward favorable DFS. Our study suggests that somatic mutations in *FAT* family genes are potential prognostic biomarkers for CRC.

## ARTICLE HIGHLIGHTS

### Research background

The human *FAT* cadherin gene family comprises the *FAT1*, *FAT2*, *FAT3* and *FAT4* genes. Somatic mutations of *FAT* family genes have been detected in different human cancers.

### Research motivation

Until now, the role of *FAT* family genes in colorectal carcinoma (CRC) tumorigenesis has not been well studied. In this study, we characterized the clinicopathologic features of *FAT* family gene mutations in CRC patients.

### Research objectives

In total, 526 CRC cases were selected from The Cancer Genome Atlas PanCancer Atlas dataset.

### Research methods

CRC cases were categorized into two groups based on their mutational status on *FAT* family genes: The cases with mutant *FAT1-4* and the cases with wild-type *FAT1-4*. Standard demographic and clinicopathological data were retrieved for each patient, including age, sex, tumor location, pT stage, pN stage, pM stage, differentiation grade, tumor type, lymphovascular invasion, month of disease-free survival and overall survival.

### Research results

The *FAT*-mutated CRC subtype is more commonly located on the right side of the colon and shows favorable clinicopathologic features, including a lower rate of positive lymph nodes and a lower rate of metastasis to another site or organ.

### Research conclusions

FAT cadherin family genes are frequently mutated in CRC, and their mutation profile defines a subtype of CRC with favorable clinicopathologic characteristics.

### Research perspectives

FAT somatic mutation is a potentially independent prognostic factor in CRC.

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## FOOTNOTES

**Author contributions:** Wang LL, Zheng W, Liu XL and Yin F collected and analyzed the data, made the tables and figures, and wrote and finalized the manuscript; and all authors have approved the final manuscript.

**Institutional review board statement:** This study is solely based on the publicly available TCGA PanCancer Atlas database. The Institutional Review Board Approval is not applicable.

**Informed consent statement:** This study is solely based on the publicly available TCGA PanCancer Atlas database. The Informed Consent Statement is not applicable.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Data sharing statement:** No additional data are available.

**STROBE statement:** The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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**S-Editor:** Wang JJ

**L-Editor:** A

**P-Editor:** Wang JJ

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