Genes & Genomics (2021) 43:1381–1388
https://doi.org/10.1007/s13258-021-01158-0

Online ISSN 2092-9293
Print ISSN 1976-9571

RESEARCH ARTICLE

Rare minisatellite alleles of *MUC2*-MS8 influence susceptibility to rectal carcinoma

So-Young Seol[1,2] · Gi-Eun Yang[1,3] · Yoon Cho[1,3] · Min Chan Kim[4] · Hong-Jo Choi[4] · Yung Hyun Choi[5] · Sun-Hee Leem[1,3]

Received: 11 July 2021 / Accepted: 14 August 2021 / Published online: 26 August 2021

Abstract

Background Previously, we identified eight novel minisatellites in the *MUC2*, of which allelic variants in *MUC2*-MS6 were examined to influence susceptibility to gastric cancer. However, studies on the susceptibility to gastrointestinal cancer of other minisatellites in the *MUC2* region still remain unprogressive.

Objective In this study, we investigated whether polymorphic variations in the *MUC2*-MS8 region are related to susceptibility to gastrointestinal cancer.

Methods We assessed the association between *MUC2*-MS8 and gastrointestinal cancers by a case–control study with 1229 controls, 486 gastric cancer cases, 220 colon cancer cases and 278 rectal cancer cases. To investigate whether intronic minisatellites affect gene expression, various minisatellites were inserted into the luciferase-reporter vector and their expression levels were examined. We also examined the length of *MUC2*-MS8 alleles in blood and cancer tissue matching samples of 107 gastric cancer patients, 125 colon cancer patients, and 85 rectal cancer patients, and investigated whether the repeat sequence affects genome instability.

Results A statistically significant association was identified between rare *MUC2*-MS8 alleles and the occurrence of rectal cancer: odds ratio (OR), 6.66; 95% confidence interval (CI), 1.11–39.96; and $P = 0.0165$. In the younger group (age, < 55), rare alleles were significant associated with an increased risk of rectal cancer (odds ratio, 24.93 and $P = 0.0001$). Suppression of expression was found in the reporter vector inserted with minisatellites, and loss of heterozygosity (LOH) of the *MUC2*-MS8 region was confirmed in cancer tissues of gastrointestinal cancer patients (0.8–5.9%).

Conclusion Our results suggest that the rare alleles of *MUC2*-MS8 could be used to identify the risk of rectal cancer and that this repeat region is related to genomic instability.

Keywords *MUC2* · Rectal cancer risk · VNTR · LOH

So-Young Seol and Gi-Eun Yang have contributed equally to this work.

✉ Sun-Hee Leem
shleem@dau.ac.kr

1 Department of Biomedical Science, Dong-A University, Busan 49315, Korea

2 Department of Medical Oncology, Gangnam Severance Cancer Hospital, Yonsei University College of Medicine, Seoul, Korea

3 Department of Health Sciences, Dong-A University, Busan 49315, Korea

4 Department of Surgery, College of Medicine, Dong-A University, Busan 49201, Korea

5 Department of Biochemistry, College of Oriental Medicine, Anti-Aging Research Center, Dong-Eui University, Busan 47227, Korea

Introduction

In general, gastrointestinal cancer (GI) includes esophageal cancer, gastric cancer, colon cancer, rectal cancer, pancreatic cancer, liver cancer, gallbladder cancer, bowel cancer, appendicitis, and anal cancer, which is noted as a major cause of cancer-related death (Bray et al. 2018). Mucins are high molecular weight epithelial glycoprotein contained in mucus and is a viscous secretion that covers the epithelial surface of the digestive or respiratory system. These mucins form the first line of physical defense and act as chemical and immunological barriers (Byrd and Bresalier 2004). Abnormal mucin expression and glycosylation are related to chronic inflammation and gastrointestinal cancer.

Twenty human mucin genes are divided into functionally secreted gel-forming mucins and transmembrane mucins, and some *MUC* gene products do not fit well in either class or have both properties (Byrd and Bresalier 2004). Among them, the *MUC2* gene encodes gel-forming mucin, located between *H-Ras* and *IGF2* on the 11p15.5 chromosome (Byrd and Bresalier 2004). It is also confirmed that the central domain of mucin has variable number of tandem repeats (VNTR, minisatellites), consisting of threonine-, serine- and proline-rich repeated peptides (Byrd and Bresalier 2004). While the effect of minisatellites on gene function is unclear, several genes (*MUC* genes, *H-Ras, hTERT,* and *Boris*) have shown susceptibility to certain diseases depending on the length of the minisatellites (Carvalho et al. 1997; Kwon et al. 2019; Kyo et al. 1999; Weitzel et al. 2000; Yoon et al. 2010a, b, 2016).

In previous work, we detected eight tandem repeats regions within *MUC2*, of which the short rare alleles of *MUC2*-MS6 were associated to gastric cancer (Jeong et al. 2007). In particular, some minisatellites regions were reported to affect gene expression (Yoon et al. 2016), and they also showed loss-of-heterozygosity (LOH) due to genomic instability during cancer development (Jeong et al. 2007; Kwon et al. 2019).

In this study, we examined the multi-allelic properties of *MUC2*-MS8, and then we identified whether there was an association between certain specific alleles of *MUC2*–MS8 and susceptibility for gastrointestinal cancer. Next, we compared the length difference of *MUC2*-MS8 in genomic DNAs from matched blood and cancer tissue obtained from patients with gastric cancer, colon cancer, or rectal cancer. Here, we suggest that *MUC2*-MS8 alleles may be associated to genomic instability and related to susceptibility to rectal cancer.

Materials and methods

Preparation of genomic DNA from peripheral blood and cancer tissues

We conducted a case–control study with genomic DNA obtained from 1229 cancer-free controls, 455 gastric cancer, 192 colon cancer, and 278 rectal cancer (Table 1). In interviews, people without a history of cancer and currently without cancer were recruited as control groups. We also isolated genomic DNAs from 107 stomach cancer patients, 125 colon cancer patients, and 85 rectal cancer patients by matching each patient's blood and cancer tissue. After obtaining approval from the bioethics committees of Dong-A University Hospital (#IRB-07-10-7; Busan, Korea), Inje University Paik Hospital (#IRB11-011; Busan, Korea) and Chungbuk National University Hospital (#IRB-2006-1; Cheongju, Korea), cancer cases and control groups were recruited.

PCR analysis of minisatellite polymorphism in *MUC2*-MS8

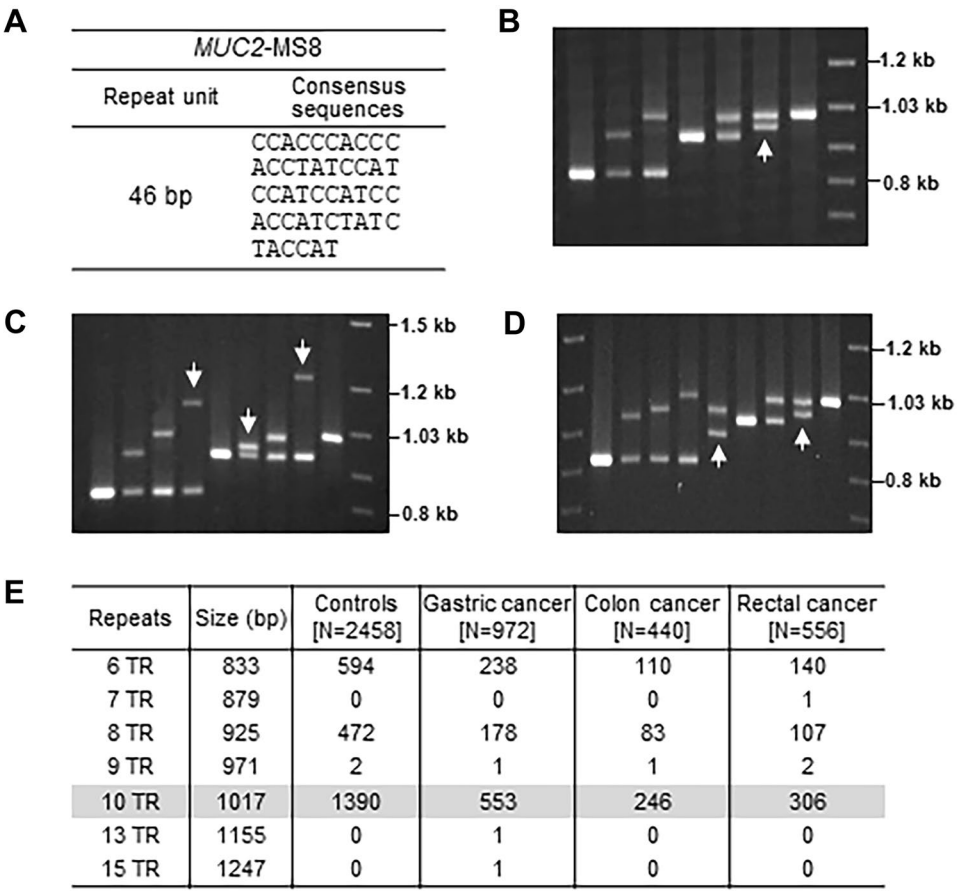
We analyzed *MUC2*–MS8 polymorphisms by PCR using primers designed in our previous study (Jeong et al. 2007); MS8, F-GTAGGCCCCACCGTGTTT & R-AGAAGCTCT GACATGACATCTTGGCC. After the PCR reaction was carried out as in the previous study (Jeong et al. 2007), PCR products were separated by gel electrophoresis using 2% SeaKem LE agarose (Cambrex, ME) (Figs. 1, 2).

Construction of the pGL3-promoter vector with *MUC2*-MS8 tandem repeats

Three common (6TR, 8TR and 10TR) allele and four rare alleles (7TR, 9TR, 13TR and 15TR) were amplified from genomic DNA from controls and cases with gastrointestinal cancers (Fig. 2). Seven different length fragments of the

Table 1 Age and sex distribution of cases and controls

Characteristic	Level	Controls [N = 1229]	GC Cases [N = 486]	CC cases, [N = 220]	RC cases, [N = 278]
Age (y)	30–49	249 (20.3)	96 (19.8)	35 (15.9)	54 (19.4)
	50–59	425 (34.6)	145 (29.8)	64 (29.1)	77 (27.7)
	60–69	328 (26.7)	159 (32.7)	72 (32.7)	94 (33.8)
	70–79	203 (16.5)	78 (17.1)	40 (18.2)	48 (17.2)
	80 +	24 (2.0)	8 (1.8)	9 (4.1)	5 (1.8)
	Average	54.84	58.94	60.84	59.95
	Median	55	59	62	61
Sex	Women	403 (32.8)	168 (34.6)	85 (38.6)	104 (37.4)
	Men	826 (67.2)	318 (65.4)	135 (61.4)	174 (62.6)



E

Repeats	Size (bp)	Controls [N=2458]	Gastric cancer [N=972]	Colon cancer [N=440]	Rectal cancer [N=556]
6 TR	833	594	238	110	140
7 TR	879	0	0	0	1
8 TR	925	472	178	83	107
9 TR	971	2	1	1	2
10 TR	1017	1390	553	246	306
13 TR	1155	0	1	0	0
15 TR	1247	0	1	0	0

Fig. 1 Haplotyic patterns of *MUC2*-MS8 minisatellites in cancer-free controls and cases with gastrointestinal cancers. **A** The consensus sequence of *MUC2*-MS8 minisatellites repeat units (Jeong et al. 2007). Comparison of haplotype patterns of *MUC2*-MS8 between controls (**B**), (Jeong et al. 2007) and patients with gastric (**C**), and rectal cancers (**D**). Rare alleles are indicated by white arrows in (**B, C**) and (**D**). Size markers (M) are given in kb. **E** The repeat number, size of the PCR products and allelic frequency in controls and gastrointestinal cases are indicated

MUC2-MS8 were amplified and inserted into *Bam*HI/*Sal*I sites (in the enhancer region) of the pGL3-Promoter vector (Promega, WI, USA), respectively. All seven different constructs were confirmed by DNA sequencing.

Cells and luciferase assay

The effect of *MUC2*-MS8 alleles on luciferase expression were investigated using 293 T [human embryonic kidney cell line, Korea Cell Line Bank (KCLB), Korea] and LoVo (colorectal cancer cell line, KCLB, Korea) cells. For the luciferase assay, cells were transfected with each construct of the seven different *MUC2*–MS8 (0.5 µg per well) as described in the previous study (Kim et al. 2021).

Statistical analyses

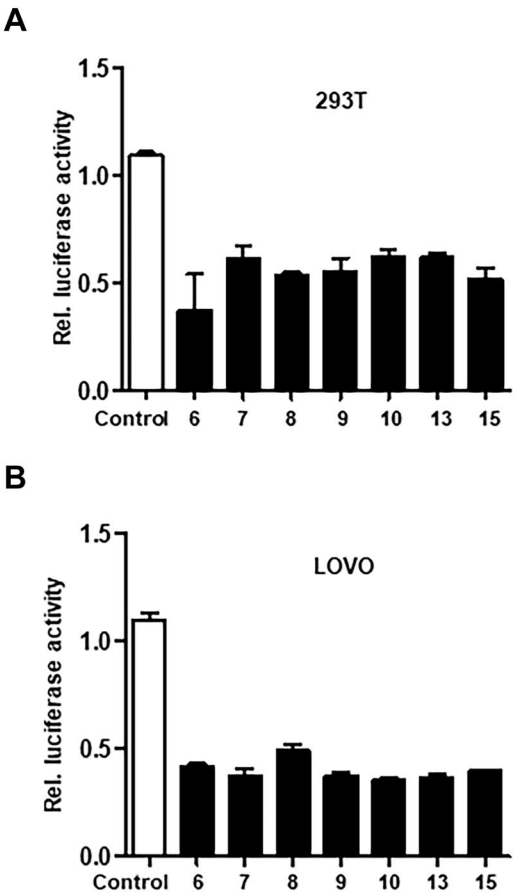
Heterozygosity was confirmed by calculating the degree of polymorphism in the *MUC2*-MS8 region in a range between 0 and 1 (Nei and Roychoudhury 1974). Odds ratio (OR) and 95% confidence interval (CI) determination and statistical significance validation were performed as described in previous studies (Jeong et al. 2007).

Results

Polymorphic analysis of *MUC2*-MS8 alleles

In a previous study, we identified nine *MUC2* minisatellites through analysis of the *MUC2* genome sequence (Jeong et al. 2007). For *MUC2*-MS8 (repeat unit 46 bp, Fig. 1A), located in Intron 40, polymorphism was identified using a cancer-free control group (Jeong et al. 2007). All identified *MUC2*-MS8 alleles can be classified as rare alleles if their frequency is less than 1%, and the rest can be classified as common alleles. In the control group, we found 4 alleles with repeat counts of 6 to 10 (6TR, 8TR, 9TR, and 10TR), with 10 repeats present as the most common allele (57%) (Jeong et al. 2007) (Fig. 1) and 9TR was identified as a rare allele (Fig. 1B) (Jeong et al. 2007).

We analyzed unrelated cancer-free individuals (1229) and cancer cases [cases with gastric cancer (486), colon cancer (220), and rectal cancer (278)] to assess the degree of polymorphism in *MUC2*-MS8 (Table 1). The heterozygosity of the *MUC2*-MS8 region ranged from 0.583 to 0.635 in the control group and the three types of cancer patient groups (controls, 0.585; gastric cancer, 0.583; colon cancer, 0.635; rectal cancer, 0.588), and there was no significant difference.



Vector	293T	
	Ave ± SE	p-value
Control	1.09 ± 0.03	Ref
6TR	0.37 ± 0.29	0.0130
7TR	0.61 ± 0.10	0.0013
8TR	0.54 ± 0.11	<0.0001
9TR	0.55 ± 0.11	0.0011
10TR	0.62 ± 0.06	0.0002
13TR	0.62 ± 0.04	<0.0001
15TR	0.52 ± 0.09	0.0004

Vector	LOVO	
	Ave ± SE	p-value
Control	1.10 ± 0.05	ref
6TR	0.42 ± 0.02	<0.0001
7TR	0.38 ± 0.05	<0.0001
8TR	0.49 ± 0.04	0.0001
9TR	0.38 ± 0.02	<0.0001
10TR	0.35 ± 0.02	<0.0001
13TR	0.37 ± 0.03	<0.0001
15TR	0.40 ± 0.01	<0.0001

Fig. 2 Effect of the *MUC2*-MS8 alleles in luciferase reporter vector. Two different cell lines [293 T (**A**) and LoVo (**B**)] were transfected with eight different vectors. As a control, the pGL3 promoter vector was used, and the other TR vectors (6TR to 15TR) are constructs inserted into the pGL3 promoter vector with varying copy numbers of the repeat unit of the *MUC2*-MS8 region. Results are showed as the ratio of activity of Firefly to Renilla luciferase. The average mean ± SE values from triplicate transfections are shown, representative of four independent experiments

We also compared the distribution and frequency of the polymorphic *MUC2*-MS8 alleles between controls (Fig. 1B) and cancer patients with gastric (Fig. 1C), rectal cancers (Figs. 1D, 2A). The identified *MUC2*-MS8 appeared as 7 different length alleles with 6–15 repeat copies and 833 bp-1247 bp in length, with the most common allele (56.37%) containing 10 repeats in total controls and cases (Fig. 1E). In this study, additional three rare alleles (cancer specific rare alleles) were confirmed that were not identified in the control group (Jeong et al. 2007): two in the gastric cancer group (13TR, 15TR; Fig. 1C, E) and one in the rectal group (7TR; Fig. 1D, E).

Genetic susceptibility of *MUC2*-MS8 rare alleles to cancer

MUC2, called intestinal mucin, is the main gel-forming intestinal mucus and a major structural component of the mucus gel (Corfield et al. 2000). This study analyzed the distribution and frequency of polymorphic *MUC2*-MS8 in gastrointestinal cancer patients to determine whether this variable minisatellite exhibits gastrointestinal cancer sensitivity. Table 2 summarizes the frequency of each *MUC2*-MS8 allele identified in cancer patients and control groups. In rectal cancer cases, the frequency of rare *MUC2*-MS8 alleles were 0.54%, compared to 0.08% in cancer-free controls. The analysis revealed a statistically significant association between the rare alleles and odds of rectal cancer (OR, 6.66; 95% CI, 1.11–39.96; $P=0.0165$). In particular, there was a significant association between the short rare alleles (< 10TR) and rectal cancer. In addition, the frequency of incidence of C/R genotypes with rare alleles also showed statistically significant values ($P=0.0164$) when comparing the rectal cancer group and the control group (Table 3). These results indicate that the rare *MUC2*-MS8 alleles is associated with the risk of rectal cancer. In other cancers, the association between rare alleles and cancer was not statistically significant but showed an increasing trend (Tables 2, 3).

Table 4 summarizes the frequency of rare *MUC2*-MS8 alleles according to age at diagnosis. In controls, no difference in the frequency of rare alleles was found between younger (< 55 years) and older individuals (≥ 55 years) ($P=0.8925$). In comparison to older patients (≥ 55 years), however, we found that younger individuals (< 55 years) with cancer had an increased OR (8.30, CI: 0.74–93.19: $P=0.0416$) of association between rare *MUC2*-MS8 alleles and rectal cancer (Table 4). In particular, a comparison of young groups in controls and

Table 2 Frequency of *MUC2*–MS8 rare alleles and risk of cancer

MS8	Alleles	Common alleles (%)				Rare alleles (%)					OR (95% CI)	*P*-value
		6	8	10	Total	7	9	13	15	Total		
Control	2458	594 (24.17)	472 (19.20)	1390 (56.55)	2456 (99.92)	0	2	0	0	2 (0.08)	1.00	-
Gastric cancer	972	238 (24.49)	178 (18.31)	553 (56.89)	969 (99.69)	0	1	1	1	3 (0.31)	3.80 (0.63–22.79)	0.1159
Colon cancer	440	110 (25.00)	83 (18.86)	246 (55.90)	439 (99.77)	0	1	0	0	1 (0.23)	2.80 (0.25–30.92)	0.3808
Rectal cancer	556	140 (25.18)	107 (19.24)	306 (55.04)	553 (99.46)	1	2	0	0	3 (0.54)	6.66 (1.11–39.96)	**0.0165**

Bold value is statistically significant ($P < 0.05$)

Table 3 Univariate ORs and 95% CIs for cancer associated with *MUC2*-MS8 rare alleles

MUC2-MS8	Total case	C/C	C/R		OR (95% CI)	*P*-value
Control	1229	1227(99.84%)	2	2 (0.16%)	1.00	–
Gastric cancer	486	483 (99.38%)	3	3 (0.62%)	3.81 (0.63–22.88)	0.1156
Colon cancer	220	219 (99.54%)	1	1 (0.46%)	2.80 (0.25–31.03)	0.3805
Rectal cancer	278	275 (98.92%)	3	3 (1.08%)	6.69 (1.11–40.25)	**0.0164**

Bold value is statistically significant ($P < 0.05$)

C/C, two common alleles; C/R, one rare allele/one common allele

Table 4 Frequency of rare alleles at *MUC2*-MS8 loci associated with age

Age#	Control	Gastric cancer	Ref[2] OR (95% CI) *P*-value	Colon cancer	Ref[2] OR (95% CI); *P*-value	Rectal cancer	Ref[2] OR (95% CI); *P*-value
< 55	1/673 (0.15%)	1/120 (0.8%)	6.4 (0.40–103.1); 0.13	0/61 (0%)	ND	2/54 (3.7%)	**24.93 (2.22–279.3) 0.0001**
≥ 55	1/556 (0.18%)	2/366 (0.5%)	3.04 (0.27–33.63); 0.3407	1/159 (0.6%)	3.50 (0.22–56.22); 0.3464	1/224 (0.4%)	2.48 (0.15–39.86); 0.5067
Ref[1] OR (95% CI) *P*-value	0.83 (0.05–13.2) 0.8925	1.53 (0.14–16.97) 0.7295		ND		**8.30 (0.74–93.19) 0.0416**	

Bold values are statistically significant ($P < 0.05$)

ND, not determined

[#]Age at diagnosis; Ref[1] (Older population in the same group); Ref[2] (the same ages of controls)

rectal cancer cases showed a significant difference in the association between rectal cancer and rare *MUC2*-MS8 allele in young patients: OR 24.93 (CI: 2.22–279.3, $P = 0.0001$). These results suggest that rare *MUC2*-MS8 alleles may be genetically associated with rectal cancer.

Possible function of *MUC2*-MS8 alleles for the expression of *MUC2*

To examine the possible role of *MUC2*-MS8 in intron regions, we constructed reporter vectors that included the seven different alleles (6TR, 7TR, 8TR, 9TR, 10TR, 13TR, and 15TR) of *MUC2*-MS8 (Fig. 2) inserted into the pGL3-Promoter vector. Then, two cell lines (293 T/HEK293T and LoVo) used to determine the effect of *MUC2*-MS8 alleles on *MUC2* expression. After transfection into 293 T and LoVo cells using these seven types of vectors, luciferase activity was investigated (Fig. 2). In 293 T cells, the activity of luciferase was significantly reduced when transfecting vectors containing TR alleles of *MUC2*-MS8 compared to when transfected with pGL3-Promoter control vector (Fig. 2). These results suggest that the repeat sequence of

MUC2-MS8 suppresses the expression of *MUC2*. Even when the colorectal cancer cell line LoVo was used, significant expression inhibition by the repeat sequence was observed (Fig. 2).

Analysis of *MUC2*-MS8 instability in gastrointestinal cancer tissues

Loss of heterozygosity (LOH) at chromosome has been found in a variety of human carcinoma, suggesting that chromosomal arrangements important to tumorigenesis (Lazar et al. 1998). Since the *MUC2* gene contains a high-density minisatellite, we investigated whether this region is involved in chromosomal instability in cancer tissues. This idea was examined by comparing the polymorphic *MUC2*-MS8 alleles in the blood and cancer tissues from the same patient with gastrointestinal cancer (107 gastric cancer, 125 colon cancer and 85 rectal cancer; Fig. 3). In genomic DNA obtained from blood and cancer tissue from the same patient with gastrointestinal cancer, there were eight cases of LOH in *MUC2*-MS8 in DNA obtained from cancer tissues (Fig. 3). When 107 gastric cancer patients were examined, the frequency of rearrangement was 2.8% (2/107) (Fig. 3A). In addition, the LOH frequency of *MUC2*-MS8 was 0.8% (1/125) in colon cancer tissues (Fig. 3B) and 5.9% (5/85) in rectal cancer tissues (Fig. 3C). The frequency of these LOH shows a trend very similar to the results of the previous cases-controls study that confirmed the association with cancer.

Discussion

Four secretion mucin genes, *MUC2*, *MUC5AC*, *MUC5B*, and *MUC6*, are clustered on chromosome 11, of which *MUC2* has high intestinal expression and *MUC5AC*, *MUC5B* and *MUC6* have high bronchial and upper gastrointestinal expression (Sylvester et al. 2001; Van Klinken et al. 1995). The main characteristic of apomucins is that they have a variable number tandem repeat (VNTR, minisatellites) sequence (Gendler and Spicer 1995; Van Klinken et al. 1995).

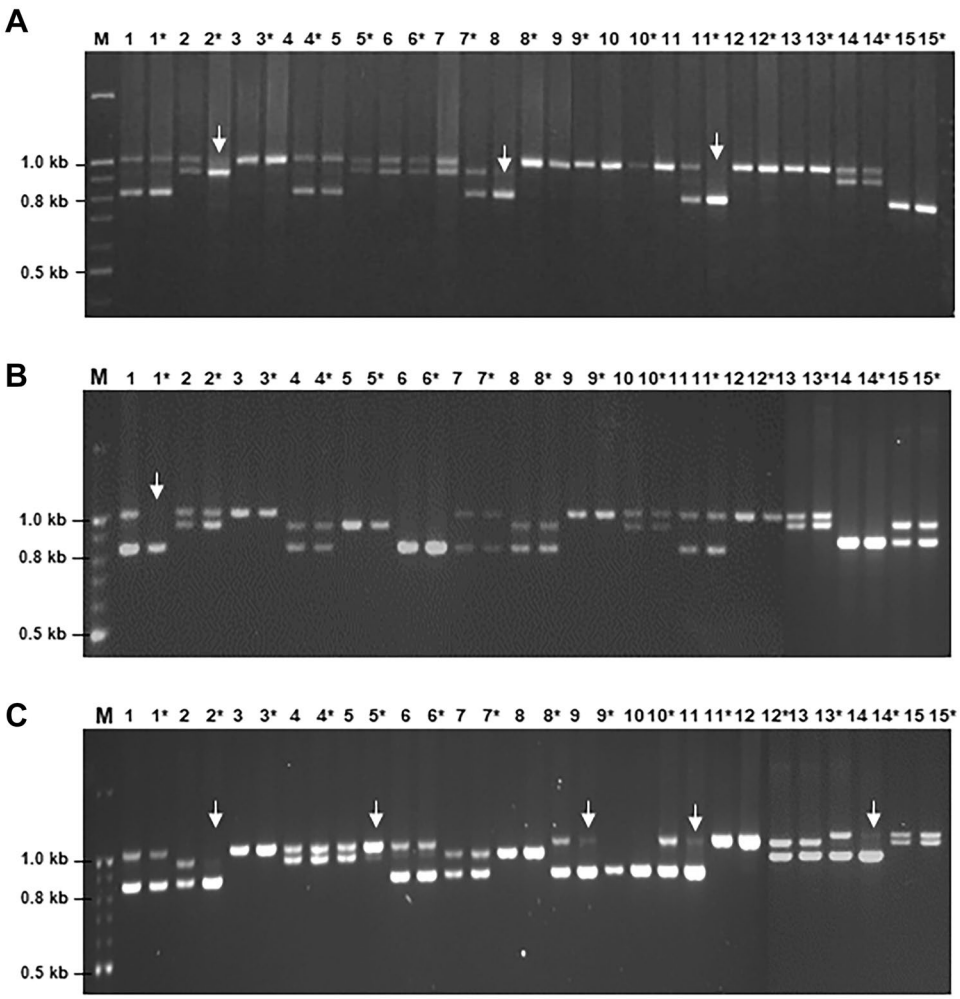


Fig. 3 LOH at *MUC2*-MS8 region in gastrointestinal cancer tissues. Comparison *MUC2*-MS8 alleles between blood and cancer tissues obtained from the same patient with gastric (**A**), colon (**B**), or rectal cancer (**C**). LOH in cancer tissues are indicated by white arrows in electrophoretic patterns. Cancer tissue samples are indicated by asterisks and M indicates the size marker

Minisatellites are tandem repeating DNA sequences distributed throughout the human genome, especially in the terminal regions of chromosomes (Jeffreys et al. 1985). Although the characteristics of these minisatellites are not clear, it has been reported that certain minisatellites are involved in chromosomal rearrangement or susceptibility to disease (Jeong et al. 2007; Kwon et al. 2019; Kyo et al. 1999). In a previous study, nine minisatellites were identified by analyzing the entire *MUC2* sequence, eight of which were identified by PCR (Jeong et al. 2007). In *MUC2*-MS8 (introns 40), we found several canonical CACGT-binding sites for the *MYC* family of oncogenic transcription factors (Jeong et al. 2007). These transcription factors located in *MUC2*-MS8 region may be related to a carcinogenesis by the regulation of *MUC2* expression. We examined whether the *MUC2*-MS8 region effects on the gene expression; we constructed vectors containing each minisatellite in enhancer regions of a reporter plasmid. Coincidence with luciferase assay, this analysis suggests that *MUC2*-MS8 is a potential region for regulation of gene expression even though it located in intron, a non-coding region (Fig. 2).

Rare alleles of minisatellites are associated high risk for various types of cancer (Jeong et al. 2007; Kwon et al. 2019; Kyo et al. 1999; Yoon et al. 2010b, 2016). Among the minisatellites of the *MUC2* gene, a short rare gene of *MUC2*-MS6 has been identified as associated with stomach cancer, and this study has identified a link between rare *MUC2*-MS8 allergies and rectal cancer. In addition, the present study indicated that the incidence of the rare *MUC2*-MS8 allele was significantly higher in younger rectal cancer patients than in younger cancer-free controls when age was considered. These results suggest that the rare *MUC2*-MS8 allele may be genetically linked.

Numerous studies have reported that genetic instability appears in human neoplasia, and that persistent genetic instability is important in the pathogenesis of all colorectal cancers (Lengauer et al. 1997, 1998). *MUC2* is located at the end of chromosome 11 and contains dense minisatellites involved in chromosome instability, and LOH mutations and microsatellite instability have also been reported in colorectal cancer (Jeong et al. 2007; Lengauer et al. 1998). We analyzed the *MUC2*-MS8 alleles in gDNA from blood and cancer tissue derived from patients with gastrointestinal cancers, and detected nine cases with LOH in *MUC2*-MS8 (Fig. 3).

Therefore, our observations show that *MUC2*-MS8 minisatellites can function as cancer risk indicators for rectal cancer and may be related to chromosomal instability. This study will provide useful references for understanding the functionality and complex genetic characteristics of *MUC2*.

Acknowledgements We sincerely appreciate the many patients and individuals who participated in this study.

Funding This work was supported by the Dong-A University research fund.

Declarations

Conflict of interest So-Young Seol, Gi-Eun Yang, Yoon Cho, Min Chan Kim, Hong-Jo Choi, Yung Hyun Choi, and Sun-Hee Leem declare that they have no conflict of interest.

Ethical approval This study was approved by the Board for Ethics in Medical Research, Dong-A University Hospital [#IRB-06-10-02 & #IRB-07-10-7; Busan, Korea] and Chungbuk National University Hospital [#IRB-2006-1; Cheongju, Korea].

References

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A (2018) Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68:394–424

Byrd JC, Bresalier RS (2004) Mucins and mucin binding proteins in colorectal cancer. Cancer Metastasis Rev 23:77–99

Carvalho F, Seruca R, David L, Amorim A, Seixas M, Bennett E, Clausen H, Sobrinho-Simoes M (1997) MUC1 gene polymorphism and gastric cancer–an epidemiological study. Glycoconj J 14:107–111

Corfield AP, Myerscough N, Longman R, Sylvester P, Arul S, Pignatelli M (2000) Mucins and mucosal protection in the gastrointestinal tract: new prospects for mucins in the pathology of gastrointestinal disease. Gut 47:589–594

Gendler SJ, Spicer AP (1995) Epithelial mucin genes. Annu Rev Physiol 57:607–634

Jeffreys AJ, Wilson V, Thein SL (1985) Hypervariable "minisatellite" regions in human DNA. Nature 314:67–73

Jeong YH, Kim MC, Ahn EK, Seol SY, Do EJ, Choi HJ, Chu IS, Kim WJ, Kim WJ, Sunwoo Y et al (2007) Rare exonic minisatellite alleles in MUC2 influence susceptibility to gastric carcinoma. PLoS ONE 2:e1163

Kim MH, Yang GE, Jeong MS, Mun JY, Lee SY, Nam JK, Choi YH, Kim TN, Leem SH (2021) VNTR polymorphism in the breakpoint region of ABL1 and susceptibility to bladder cancer. BMC Med Genom 14:121

Kwon JA, Jeong MS, Yoon SL, Mun JY, Kim MH, Yang GE, Park SH, Chung JW, Choi YH, Cha HJ et al (2019) The hTERT-VNTR2-2(nd) alleles are involved in genomic stability in gastrointestinal cancer. Genes Genom 41:1517–1525

Kyo K, Parkes M, Takei Y, Nishimori H, Vyas P, Satsangi J, Simmons J, Nagawa H, Baba S, Jewell D et al (1999) Association of ulcerative colitis with rare VNTR alleles of the human intestinal mucin gene, MUC3. Hum Mol Genet 8:307–311

Lazar AD, Winter MR, Nogueira CP, Larson PS, Finnemore EM, Dolan RW, Fuleihan N, Chakravarti A, Zietman A, Rosenberg CL (1998) Loss of heterozygosity at 11q23 in squamous cell carcinoma of the head and neck is associated with recurrent disease. Clin Cancer Res 4:2787–2793

Lengauer C, Kinzler KW, Vogelstein B (1997) Genetic instability in colorectal cancers. Nature 386:623–627

Lengauer C, Kinzler KW, Vogelstein B (1998) Genetic instabilities in human cancers. Nature 396:643–649

Nei M, Roychoudhury AK (1974) Sampling variances of heterozygosity and genetic distance. Genetics 76:379–390

Sylvester PA, Myerscough N, Warren BF, Carlstedt I, Corfield AP, Durdey P, Thomas MG (2001) Differential expression of the chromosome 11 mucin genes in colorectal cancer. J Pathol 195:327–335

Van Klinken BJ, Dekker J, Buller HA, Einerhand AW (1995) Mucin gene structure and expression: protection vs. adhesion. Am J Physiol 269:G613-627

Weitzel JN, Ding SF, Larson GP, Nelson RA, Goodman A, Grendys EC, Ball HG, Krontiris TG (2000) The HRAS1 minisatellite locus and risk of ovarian cancer. Can Res 60:259–261

Yoon SL, Jung SI, Do EJ, Lee SR, Lee SY, Chu IS, Kim WJ, Jung J, Kim CS, Cheon SH et al (2010a) Short rare hTERT-VNTR2-2nd alleles are associated with prostate cancer susceptibility and influence gene expression. BMC Cancer 10:393

Yoon SL, Kim DC, Cho SH, Lee SY, Chu IS, Heo J, Leem SH (2010b) Susceptibility for breast cancer in young patients with short rare minisatellite alleles of BORIS. BMB Rep 43:698–703

Yoon SL, Roh YG, Chu IS, Heo J, Kim SI, Chang H, Kang TH, Chung JW, Koh SS, Larionov V et al (2016) A polymorphic minisatellite region of BORIS regulates gene expression and its rare variants correlate with lung cancer susceptibility. Exp Mol Med 48:e246