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Original Article

Association study between *OCTN1* functional haplotypes and Crohn's disease in a Korean population

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ABSTRACT Crohn's disease (CD) is a chronic inflammatory bowel disease with multifactorial causes including environmental and genetic factors. Several studies have demonstrated that the organic cation/carnitine transporter 1 (*OCTN1*) non-synonymous variant L503F is associated with susceptibility to CD. However, it was reported that L503F is absent in Asian populations. Previously, we identified and functionally characterized genetic variants of the *OCTN1* promoter region in Koreans. In that study, four variants demonstrated significant changes in promoter activity. In the present study, we determined whether four functional variants of the *OCTN1* promoter play a role in the susceptibility to or clinical course of CD in Koreans. To examine it, the frequencies of the four variants of the *OCTN1* promoter were determined by genotyping using DNA samples from 194 patients with CD and 287 healthy controls. Then, associations between genetic variants and the susceptibility to CD or clinical course of CD were evaluated. We found that susceptibility to CD was not associated with *OCTN1* functional promoter variants or haplotypes showing altered promoter activities in *in vitro* assays. However, *OCTN1* functional promoter haplotypes showing decreased promoter activities were significantly associated with a penetrating behavior in CD patients (HR=2.428, p=0.009). Our results suggest that the *OCTN1* functional promoter haplotypes can influence the CD phenotype, although these might not be associated with susceptibility to this disease.

INTRODUCTION

Organic cation/carnitine transporter (OCTN) of the solute carrier (SLC) 22 family has two isoforms in humans, OCTN1 and OCTN2 [1]. OCTN1, which is encoded by *SLC22A4*, is expressed in various organs, including the bone marrow, gut, heart, kidney, and lung [1]. OCTN1 transports various endogenous substances or drugs, including ergothioneine, carnitine, tetraethylammonium, and gabapentin, in a sodium- or pH-dependent manner according to the features of the substrates [1-5]. Although the physiological role of OCTN1 is not yet well established, previous studies have suggested that this transporter accumulates the anti-oxidant ergothioneine for protecting the body against oxidative stress [1,5].

Few studies have investigated the role of the genetic variants of *OCTN1* in the expression or transport activity of this transporter. Toh et al. [6] identified four single nucleotide polymorphisms (SNPs) of *OCTN1* that impair transport activity. In addition, Tahara et al. [7] investigated the functions and effects of SNPs in the proximal promoter region of *OCTN1*, and determined that all *OCTN1* haplotypes identified in their study population showed promoter activity comparable to that of the reference. Previously,

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we identified and functionally characterized novel *OCTN1* promoter variants in Koreans [8]. In that study, we observed that four promoter SNPs resulted in significantly altered promoter activity, compared to the reference. Two of them, g.–1875T>A and g.–1745A>G, demonstrated increased promoter activity, whereas the other two, g.–1145A>G and g.–248C>G, demonstrated decreased promoter activity. Very few studies have investigated the effect of *OCTN1* genetic variants on the response or pharmacokinetics of drugs. Urban et al. [2] reported that *OCTN1* genetic variants could impact the pharmacokinetics of the anti-epilepsy drug, gabapentin. They found that a non-synonymous variant of *OCTN1*, L503F demonstrated decreased transport activity for gabapentin, and subjects who were homozygous for this variant demonstrated significantly decreased renal secretion of gabapentin.

Crohn's disease (CD) is a chronic idiopathic inflammatory bowel disease that could involve the whole gastrointestinal tract. Although the pathogenesis of CD remains unclear, it is accepted that CD can be induced by abnormal immune responses against gut flora, in particular, in genetically susceptible individuals [9]. To date, a large number of studies have examined the association between genetic variants and susceptibility to or clinical phenotypes of CD, and many genes, such as *NOD2*, *ATG16L1*, *IRGM*, *IBD5*, and *TNFSF15* were shown to be significantly associated with CD [10-13]. In the case of *OCTN*, Peltekova et al. [4] reported an association between the TC haplotype of *OCTN*s consisting of two genetic variants, *OCTN1*, L503F and *OCTN2*, g.–207G>C and susceptibility to CD. This finding was validated by several other association studies [14-22]. However, previous studies reported that these two variants are not found in Asian populations [17-19]. In particular, to our knowledge, no other study has investigated the association between genetic variants in the *OCTN1* promoter as well as susceptibility to CD. Therefore, in the present study, we investigated whether the genetic variants of the *OCTN1* promoter that demonstrated altered promoter activity in our previous study could affect the susceptibility to or clinical course of CD in Koreans.

METHODS

Subjects

The study protocol was reviewed and approved by the Institutional Review Board of the Ewha Medical Center, Seoul, Korea, and the Institutional Review Board of Severance Hospital at Yonsei University Health System, Seoul, Korea. After receiving written informed consent, DNA samples were obtained from 194 Korean patients with CD. Those diagnosed with CD had at least a 24-month follow-up period with assessment by internal medicine specialists. The CD patients were subgrouped according to age of onset, location, and disease behavior using the Montreal Classification [23]. Among disease behaviors, "penetrating behavior" refers to the presence of intestinal perforation, intra-abdominal fistula, or inflammatory mass and/or abscess. For the control group, DNA samples were collected from 287 unrelated healthy Koreans who had no evidence of abnormalities during routine gastrointestinal examinations, showed no gastrointestinal symptoms and took no regular medications at Severance Hospital. Clinical data were obtained by reviewing the medical records.

Genetic analysis of *OCTN1*

In the present study, four *OCTN1* promoter variants, g.–1875T>A, g.–1745A>G, g.–1145A>g, and g.–248C>G, which showed significant changes in promoter activity in our previous study [8], were genotyped by a SNaPshot assay using an automated DNA analyzer (DNA Link, Inc., Seoul, Korea).

Statistical analysis

To compare the frequency of *OCTN1* genetic variations or haplotypes between patients and control groups, a χ^2-test was conducted. Comparisons of the characteristics between patient groups according to *OCTN1* functional haplotypes were analyzed using the χ^2-test and t-test. The effects of the *OCTN1* functional haplotypes on the clinical course (disease behavior, azathioprine or anti-TNF agent use, and surgery) of CD were initially investigated using the Kaplan-Meier estimator and log-rank test to consider time to clinical events. Then, the multivariate Cox proportional hazards regression analysis (for each clinical parameter) was performed with adjustment for sex and age of onset.

Table 1. Comparison of the frequency of *OCTN1* variants between patients with CD and controls

Variant		Patient, n (%)	Control, n (%)	p value
g.–1875T>A	+/+	110 (56.7)	158 (55.1)	0.753
	+/–	74 (38.1)	116 (40.4)	(0.721)
	–/–	10 (5.2)	13 (4.5)	
g.–1745A>G	+/+	96 (49.5)	134 (46.7)	0.259
	+/–	75 (38.7)	128 (44.6)	(0.547)
	–/–	23 (11.9)	25 (8.7)	
g.–1145A>G	+/+	30 (15.5)	37 (12.9)	0.394
	+/–	78 (40.2)	134 (46.7)	(0.424)
	–/–	86 (44.3)	116 (40.4)	
g.–248C>G	+/+	30 (15.5)	36 (12.5)	0.438
	+/–	78 (40.2)	134 (46.7)	(0.361)
	–/–	86 (44.3)	117 (40.8)	

The p values were obtained using a recessive (+/+ or +/- vs. -/-) model. The p values in parenthesis were obtained from analyses using the dominant (+/+ vs. +/- or -/-) model.

RESULTS

Association between *OCTN1* genotypes or haplotypes and susceptibility to CD

We compared the frequencies of *OCTN1* functional variants or haplotypes reported in our previous study [8] between patients with CD and healthy control groups. Table 1 shows the frequency of the four variants between the two groups. We observed that there was no significant difference in the frequency of any of the genetic variants analyzed between the two groups. Using genotype data, haplotypes were assembled using the Haploview program (version 4.3, Broad Institute, Cambridge, MA, USA). There were six promoter haplotypes in our population. The frequency of each haplotype in CD patient and control groups is listed in Table 2. We observed that the frequency of haplotypes in CD patients was comparable with those of the control group. These findings indicate that the susceptibility to CD might not be affected by *OCTN1* functional variants or haplotypes in Koreans.

Effect of the *OCTN1* functional promoter haplotype on the clinical characteristics of patients with CD

Next, we examined whether the functional promoter haplotypes of *OCTN1* could affect the clinical characteristics of patients with CD, although we found that these haplotypes did not affect susceptibility to CD. Here, we hypothesized that the *OCTN1* functional haplotypes that demonstrated decreased promoter activity could be associated with a severe clinical course of CD, as the well-known *OCTN1* variant L503F demonstrated a reduction in transport activity in a previous study [4]. In our population, five *OCTN1* promoter haplotypes, (H2 to H6) were predicted to have decreased promoter activity according to the results of our previous study [8]. Therefore, we divided the 194 patients into two groups according to the five *OCTN1* haplotypes: a variant group (n=86) and a control group (n=108). The variant group consisted of subjects having two of five promoter haplotypes, and the control group consisted of subjects who were not members of the variant group. First, we compared the demographic or clinical characteristics of CD patients and observed that the functional haplotypes showing decreased *OCTN1* promoter activity were not associated with sex, age of

Table 2. Comparison of the frequency of *OCTN1* haplotypes between patients with CD and controls

ID	g.–1875T>A	g.–1745A>G	g.–1145A>G	g.–248C>G	Patient, n (%)	Control, n (%)	p value
H1	T	A	A	C	138 (35.6)	206 (35.9)	0.919
H2	T	**G**	**G**	**G**	120 (30.9)	178 (31.0)	0.979
H3	**A**	A	**G**	**G**	93 (24)	142 (24.7)	0.786
H4	T	A	**G**	**G**	36 (9.3)	46 (8.0)	0.492
H5	T	A	A	**G**	0 (0)	2 (0.3)	0.245
H6	**A**	**G**	**G**	**G**	1 (0.3)	0 (0)	0.250

The SNPs were marked in bold-faced letters.
The minor alleles were underlined.

Table 3. Demographic and clinical characteristics of patients according to *OCTN1* haplotypes

Parameter	Variant (%)	Control (%)	Variant mean±SD	Control mean±SD	p value
Total number	86	108			
Sex, male	59 (68.6)	83 (76.9)			0.198
Age of onset (years)[a]			25.24±9.96	25.05±9.50	0.883
≤16	7 (8.1)	8 (7.4)			
16< <40	74 (86.0)	92 (85.2)			0.896
≥40	5 (5.8)	8 (7.4)			
Body mass index			19.90±3.00	20.04±3.11	0.760
Location[a]					
Ileal (L1)±L4	24 (27.9)	18 (16.7)			
Colonic (L2)±L4	15 (17.4)	13 (12.0)			0.054
Ileocolonic (L3)±L4	47 (54.7)	77 (71.3)			
Perianal fistula	36 (41.9)	58 (53.7)			0.101

[a]According to the Montreal Classification [23].
L4 indicates upper gastrointestinal involvement.
SD, standard deviation.

onset, body mass index, or disease location in Korean patients with CD (Table 3). Then, we examined the association between *OCTN1* functional promoter haplotypes and clinical course of CD. We found that *OCTN1* haplotypes significantly affected the time to development of a penetrating disease behavior (log-rank p=0.008, Fig. 1), while other clinical events such as usage of azathioprine or anti-TNF agents or surgery were not affected by the haplotypes (data not shown). The risk of a penetrating behavior was significantly higher in patients in the variant group compared to the control group (hazards ratio (HR)=2.428, p=0.009) after adjustment for sex and age of onset in a Cox proportional hazards model (Table 4). The usage of azathioprine or anti-TNF agents and need for surgery were comparable between the two groups.

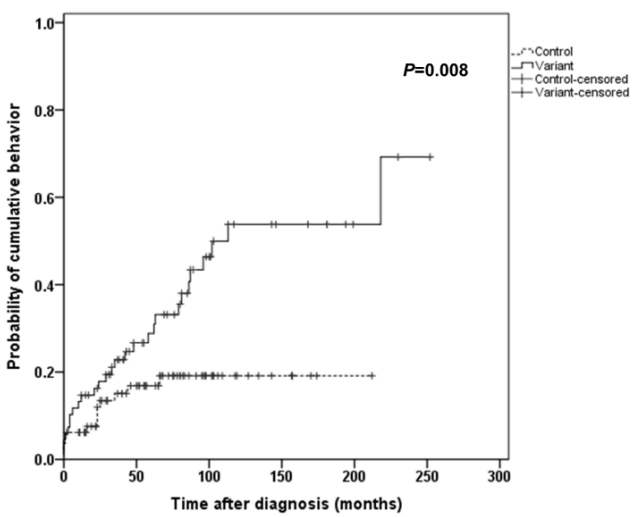

Fig. 1. Kaplan-Meier curve for developing a penetrating disease behavior in Korean CD patients during follow-up. The log-rank test was performed between the *OCTN1* variant (solid line) and control (dashed line) groups (p=0.008).

DISCUSSION

Crohn's disease (CD) is a chronic relapsing inflammatory disease and its incidence and prevalence are increasing with time [24]. Although the etiopathogenesis of CD is unclear, it is well accepted that this disease could be caused by dysregulated immune responses in genetically susceptible subjects [9]. Previous genome-wide or genotype-phenotype association studies have reported a significant association between genetic variants and susceptibility to or clinical phenotypes of CD [10-13]. In particular, it was shown that several genetic variants of *IL12B*, *TNFSF15*, *IL23R*, and *ATG16L2* were associated with susceptibility to or phenotypes of CD in Koreans [25-27]. The TC haplotype consisting of *OCTN1*, L503F and *OCTN2*, g.–207G>C was shown to be a predictor of CD development [4]. Several studies have found that L503F and –207G>C are ethnic-specific variants. For example, it has been reported that the frequencies of L503F and –207G>C were 0.412 and 0.500, respectively, in Europeans [7,28]. In those studies, the frequencies of these variants were also high in Mexicans: the frequencies of L503F and –207G>C were 0.230 and 0.679, respectively. However, interestingly, both are absent in Asian populations [17-19]. Recently, we reported that the functional haplotype of the *OCTN2* promoter was associated with the clinical course in Korean CD patients [29]. In that study, compared to the controls, we observed much higher frequencies of a penetrating behavior and need for surgery in patients with the *OCTN2* haplotype showing decreased promoter activity.

In the present study, we evaluated the clinical usefulness of *OCTN1* functional haplotypes identified in our previous study [8]. First, we investigated the association between genetic variants of the *OCTN1* promoter and CD. The four variants showing significant changes in promoter activity in our previous study were not associated with susceptibility to CD in Koreans. In addition, the frequencies of all variants or haplotypes were comparable between patients and healthy controls. Vermeire et al. [30] previously reported that *OCTN1*, L503F was not associated with susceptibility to inflammatory bowel diseases, including CD, but was associated with the clinical phenotypes of

Table 4. Clinical course of patients according to *OCTN1* haplotypes

Parameter	Variant (%)	Control (%)	Hazards ratio[b] (95% CI)	p value
Total number	86	108		
Behavior[a]				
Inflammatory	40 (46.5)	68 (63.0)		
Stricturing	18 (20.9)	27 (25.0)	1.004[c] (0.549~1.837)	0.990
Penetrating	28 (32.6)	13 (12.0)	2.428[c] (1.243~4.741)	0.009
Azathioprine or Anti-TNF agent use	64 (74.4)	81 (75.0)	0.795 (0.566~1.115)	0.184
Surgery	33 (38.4)	32 (29.6)	1.147 (0.702~1.875)	0.584

[a]According to the Montreal Classification. [b]After adjustment for other covariates (i.e., sex and age of onset). [c]HR of a multivariate Cox proportional hazards regression model with the inflammatory type as a reference category for the outcome variable.
CI, confidence interval.

the disease, particularly perianal or penetrating complications in the population that was studied. Therefore, we next examined whether *OCTN1* functional promoter haplotypes could affect CD phenotypes. Previous studies reported that OCTN1 is expressed in the intestinal epithelium and plays a protective role against oxidative stress by transporting the anti-oxidant, ergothioneine [31,32]. Another study reported that the expression of OCTN2 was increased in inflamed areas in order to compensate for cellular damage [33]. Therefore, we hypothesized that patients with decreased OCTN1 activity by genetic variants would be susceptible to intestinal inflammation, and would demonstrate more severe CD phenotypes than patients with normal OCTN1 activity. In our previous study, we determined that the *OCTN1* haplotypes that contain two variants, g.–1145A>G and g.–248C>G, showed reduced promoter activity [8]. Among the six *OCTN1* promoter haplotypes in the present study, five haplotypes (H2 to H6) contained these variants. Therefore, we compared the characteristics or clinical course of patients according to these five haplotypes. We found that the frequency of a penetrating behavior was much higher in patients in the variant group.

There are several limitations in the present study. First, the sample number of our study population was relatively small. In this study, we could not find any significant effect of *OCTN1* genotypes or haplotypes on susceptibility to CD. Validation with a larger number of patients of various ethnic groups is necessary to confirm these negative associations. Second, because the analysis of the genotype-phenotype of CD was performed retrospectively in the present study, we could not consider environmental factors in our analysis. However, we compared smoking history in some patients according to the *OCTN1* functional haplotypes; there was no significant difference in the number of smokers (30.9% of 62 patients in the variant group vs. 39.4% of 71 patients in the control groups, p=0.290).

In conclusion, we found that *OCTN1* functional promoter haplotypes could affect the clinical phenotype of CD in Koreans, although the susceptibility to CD was unrelated to *OCTN1* genotypes or haplotypes. To our knowledge, this is the first study to examine the association between CD and genetic variants of the *OCTN1* promoter. The presence of these haplotypes may be an important predisposing factor for developing a penetrating behavior in CD.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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