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BRIEF ARTICLE

# -449 C>G polymorphism of *NFKB1* gene, coding nuclear factor-kappa-B, is associated with the susceptibility to ulcerative colitis

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## Abstract

**AIM:** To clarify the association between a polymorphism -449 C>G (rs72696119) in 5′-UTR of *NFKB1* with ulcerative colitis (UC).

**METHODS:** The studied population comprised 639 subjects, including patients with UC (UC cases, *n* = 174) and subjects without UC (controls, *n* = 465). We employed polymerase chain reaction-single strand conformation polymorphism to detect the gene polymorphism.

**RESULTS:** The rs72696119 G allele frequencies in controls and UC cases were 33.4% and 38.5%, respectively (*P* = 0.10). Genotype frequency of the GG homozygote in UC cases was significantly higher than that in controls (*P* = 0.017), and the GG homozygote was significantly associated with susceptibility to UC [odds ratio (OR), 1.88; 95%CI, 1.13-3.14]. In male subjects, the GG homozygote was associated with an increased risk for UC (OR, 3.10; 95%CI, 1.47-6.54; *P* = 0.0053), whereas this association was not found in female subjects. In addition, the GG homozygote was significantly associated with the risk of non-continuous disease (OR, 2.06; 95%CI, 1.12-3.79; *P* = 0.029), not having total colitis (OR, 2.40; 95%CI, 1.09-3.80, *P* = 0.040), disease which developed before 20 years of age (OR, 2.80; 95%CI, 1.07-7.32, *P* = 0.041), no hospitalization (OR, 2.28; 95%CI, 1.29-4.05; *P* = 0.0090) and with a maximum of 8 or less on the UCDAI score (OR, 2.45; 95%CI, 1.23-4.93; *P* = 0.022).

**CONCLUSION:** Our results provide evidence that *NFKB1* polymorphism rs72696119 was significantly associated with the development of UC. This polymorphism influences the susceptibility to and pathophysiological features of UC.



**Key words:** Genetic polymorphism; *NFKB1*; Ulcerative colitis

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## INTRODUCTION

Ulcerative colitis (UC) is precipitated by a complex interaction of environmental, genetic, and immunoregulatory factors[1,2]. UC affects the colon and rectum and typically involves the innermost lining mucosa, manifesting as continuous areas of inflammation, with no segments of normal mucosa[3]. The pathogenesis of UC is only partially understood. Recently, the important role of innate immune response in the pathogenesis of UC has been reported[4]. In addition, some genes are associated with UC itself[5]. We have previously investigated the association between genetic polymorphisms in several genes and susceptibility to UC[6-9].

One of the linkage regions for inflammatory bowel diseases (IBD) has been mapped to chromosome 4q[10]. In this region, the *NFKB1*, encoding 2 subunits (p50 and p105) of nuclear factor r (NF)-κB, is located (4q24)[11]. NF-κB is a pleiotropic transcription factor involved in diverse immunologic processes including regulation of the intestinal immune system[12]. Dysregulation of NF-κB has been demonstrated in different inflammatory disorders, including UC[13]. Recently, many studies have reported the association between polymorphism rs28362491 (-94 ins/del ATTG of *NFKB1*) and various inflammatory diseases[14]. However, these studies have not always led to the same conclusions. Furthermore, a genetic variation, rs72696119 (-449 C>G in 5'-UTR of *NFKB1*), has been identified. We previously reported a close association between *NFKB1* polymorphisms (rs28362491 and rs72696119) and aberrant gene methylation in gastric mucosa[15].

In this study, we attempted to clarify the association between the *NFKB1* polymorphism, rs72696119 (-449 C>G), and susceptibility to UC.

## MATERIALS AND METHODS

### Clinical samples

The studied population comprised 639 subjects, including patients with UC (UC cases, $n$ = 174), who were enrolled in Fujita Health University Hospital, and subjects without UC (controls, $n$ = 465). The diagnosis of UC was based on standard clinical, endoscopic, radiological, and histological criteria[16]. The control subjects had no lower abdominal symptoms, diarrhea or hematochezia. Genomic DNA was isolated from peripheral blood using the FlexiGene DNA Kit (QIAGEN GmbH, Hilden, Germany).

The Ethics Committees of Fujita Health University and Kanazawa Medical University approved the protocol, and written informed consent was obtained from all the participating subjects.

### Classification

According to their clinical courses, UC cases were classified into continuous disease and non-continuous disease (relapsing and only one episode)[17]. UC patients were also classified as having total colitis or not having total colitis (left sided, distal colitis and proctitis) according to the location and extension of the inflammatory lesions judged by endoscopic findings.

### Genotyping of polymorphisms

The polymorphism was genotyped by polymerase chain reaction (PCR)-single strand conformation polymorphism (SSCP) as previously reported[15,18]. To detect *NFKB1* rs72696119 C>G, using the primer pairs (449F: 5'-cgtgtgtccgtctgtctgtatgctc-3' and 449R: 5'-cgctggtgcacttctctctctttct-3'), was carried out in a volume of 20 μL containing 0.1 μg of genomic DNA. The DNA was denatured at 95 ℃ for 3 min, followed by 35 cycles at 95 ℃ for 30 s, 57 ℃ for 40 s, and 72 ℃ for 45 s, with final extension at 72 ℃ for 5 min. SSCP was carried out at 6 ℃ using a GenePhor DNA separation system with GeneGel Excel 12.5/24 (Amersham Biosciences Corp., United States), after which the denatured single strand DNA bands were detected using a DNA Silver Staining Kit (Amersham Biosciences Corp.).

### Statistical analysis

Patient age was expressed as mean ± SD. Mean age between the 2 groups was compared by Student's $t$-test. Allelic and genotype frequencies were calculated by direct counting. The allele counts and the distribution of genotypes were compared between the cases and the controls by a 2 × 2 table using Fisher's extract test. Furthermore, the strength of the association between allele frequencies and the disease was assessed by calculating the odds ratio (OR) and 95%CI. For all analyses, the level of significance was set at $P < 0.05$.

## RESULTS

### Characteristics of subjects and the frequencies of genotypes

As shown in Figure 1, single strand DNA was clearly separated by SSCP. *NFKB1* rs2505901 was in Hardy-Weinberg equilibrium ($P$ = 0.26). The mean age of the controls was significantly higher than that of UC cases (Table 1). The minor allele frequencies of rs72696119 were 33.4% and 38.5% in controls and UC cases, re-

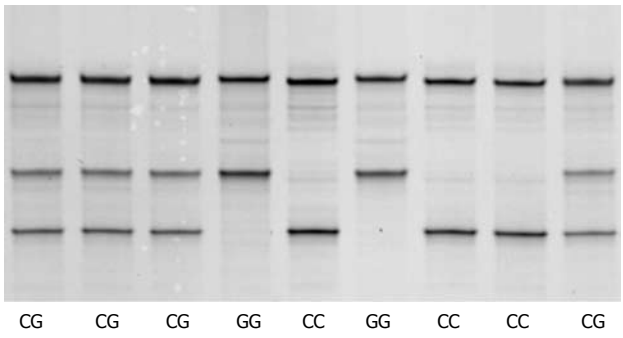


**Figure 1 Polymerase chain reaction-single strand conformation polymorphism images using clinical samples.** Single strand DNA was clearly separated by single strand conformation polymorphism.

**Table 1 Characteristics of the subjects and allelic frequency**

| | Controls | UC cases | *P* value |
|---|---|---|---|
| Number of sample | 465 | 174 | |
| Age (mean ± SD) | 50.6 ± 17.3 | 40.3 ± 13.9 | < 0.0001 |
| (age of onset) | | (33.0 ± 13.4) | |
| Male:female | 253:212 | 98:76 | NS |
| rs72696119 C>G | | | |
| C/C | 197 | 68 | |
| C/G | 225 | 78 | |
| G/G | 43 | 28 | 0.017 |
| G allele frequency | 33.40% | 38.50% | 0.10 |

UC: Ulcerative colitis; NS: Not significant.

spectively ($P$ = 0.10). The genotype frequencies of the rs72696119GG homozygote was significantly higher in UC cases than in controls ($P$ = 0.017).

### *Association between rs72696119 and UC*

The rs72696119GG homozygote was significantly associated with increased risk for UC (OR, 1.88; 95%CI, 1.13-3.14; $P$ = 0.017, Table 2). This association was stronger in male subjects (OR, 3.10; 95%CI, 1.47-6.54; $P$ = 0.0053), whereas it was not observed in female subjects.

### *Association between rs72696119 and phenotypes of UC*

The rs72696119 was associated with UC cases with an onset age below 20 years (OR, 2.80; 95%CI, 1.11-7.14; $P$ = 0.041, Table 3). In addition, the GG homozygote was significantly associated with non-continuous disease (OR, 2.06; 95%CI, 1.13-3.77; $P$ = 0.029), not having total colitis (OR, 2.04; 95%CI, 1.10-3.78; $P$ = 0.040), no hospitalization (OR, 2.28; 95%CI, 1.29-4.05; $P$ = 0.0090), and with a maximum of 8 or less on the UCDAI score (OR, 2.45; 95%CI, 1.23-4.93; $P$ = 0.022). This polymorphism was not associated with response to steroid treatment.

## DISCUSSION

In the current study, we evaluated the association between the polymorphism rs72696119 (-449C>G) in

**Table 2 Association between rs72696119 and ulcerative colitis**

| | Genotype (*n*) | | | GG *vs* others | |
|---|---|---|---|---|---|
| Overall | C/C | C/G | G/G | OR (95%CI) | *P* value |
| Controls (465) | 197 | 225 | 43 | Ref. | - |
| UC cases (174) | 68 | 78 | 28 | 1.88 (1.13-3.14) | 0.017 |
| Male | | | | | |
| Controls (253) | 102 | 136 | 15 | Ref. | - |
| UC cases (98) | 40 | 42 | 16 | 3.10 (1.47-6.54) | 0.0053 |
| Female | | | | | |
| Controls (212) | 95 | 89 | 28 | Ref. | - |
| UC cases (76) | 28 | 36 | 12 | 1.23 (0.592-2.57) | 0.57 |

UC: Ulcerative colitis; OR: Odds ratio.

**Table 3 Association between rs72696119 and phenotype of ulcerative colitis**

| | Genotype (*n*) | | | GG *vs* others | |
|---|---|---|---|---|---|
| | CC | CG | GG | OR (95%CI) | *P* value |
| Controls (465) | 197 | 225 | 43 | Ref. | - |
| Age of onset | | | | | |
| ≤ 20 (27) | 12 | 9 | 6 | 2.80 (1.07-7.32) | 0.041 |
| 21 ≤ (133) | 50 | 66 | 17 | 1.44 (0.791-2.62) | 0.25 |
| Clinical type | | | | | |
| Not continuous (98) | 34 | 47 | 17 | 2.06 (1.13-3.77) | 0.029 |
| Continuous (71) | 32 | 30 | 9 | 1.43 (0.662-3.07) | 0.39 |
| Extension | | | | | |
| Not total colitis (93) | 31 | 46 | 16 | 2.04 (1.09-3.80) | 0.040 |
| Total colitis (78) | 35 | 32 | 11 | 1.61 (0.792-3.28) | 0.22 |
| Max UCDAI score | | | | | |
| ≤ 8 (60) | 20 | 28 | 12 | 2.45 (1.23-4.93) | 0.022 |
| 9 ≤ (106) | 44 | 49 | 13 | 1.37 (0.716-2.63) | 0.37 |
| Hospitalization | | | | | |
| None (106) | 41 | 45 | 20 | 2.28 (1.29-4.05) | 0.0090 |
| One time ≤ (60) | 25 | 30 | 5 | 0.892 (0.350-2.28) | 1.00 |
| Response to treatment | | | | | |
| Steroid-dependent (34) | 13 | 17 | 4 | 1.31 (0.440-3.89) | 0.54 |
| Steroid-refractory (46) | 18 | 23 | 5 | 1.20 (0.449-3.19) | 0.79 |

OR: Odds ratio.

5'-UTR of *NFKB1* and the risk for developing UC. The rs72696119 GG homozygote was significantly associated with increased risk for UC, especially in male subjects. In addition, this genotype was associated with younger age at onset, non-continuous disease, not having total colitis, no hospitalization and with a UCDAI score below 8. These results suggest that this genotype may be associated with UC of comparatively mild or moderate severity. In our study, sample selection may have affected the outcome, as our controls included patients who came to hospital in order to have treatment for complaints other than diarrhea, bloody feces and lower abdominal discomfort, and were not completely healthy subjects. Moreover, the effect of type II error cannot be excluded in relatively small sample sizes. Another limitation of this study was that mean age was different between the controls and UC cases. However, it seems that this was not an obstacle in the analysis, as UC developed at a

relatively young age.

To the best of our knowledge, there have been no reports on the distribution of rs72696119 in Japanese subjects, including HapMap-JPT. In a previous study, we demonstrated that rs72696119 has a strong allelic association with rs28362491[15]. It has been reported that the rs28362491 ATTG deletion variant in the promoter region destroys a transcription factor binding site, resulting in lower expression of NF-κB[19]. Therefore, NF-κB expression is considered to be low in rs72696119 GG variants, as well as rs28362491 del/del variants. Due to their important role in inflammation, the lower expression of NF-κB protein seems to suppress inflammation. However, several studies have shown that the rs28362491 ATTG deletion variant is associated with increased risk for the development of inflammatory or auto-immune diseases[19,20]. Our results also indicated that the rs72696119 GG homozygote was associated with an increased risk for UC in Japanese.

NF-κB names a number of different transcription factors that are homo- or heterodimers of p65, p50, p105, C-rel and relB[21]. *NFKB1* encodes both the subunits p105 and p50 of the transcription factor NF-κB by alternative splicing[22]. NF-κB is involved in both inflammatory and anti-inflammatory processes[23]. The role of NF-κB in inflammation is determined by subunit type. As part of the p65/p50 NF-κB transcription factor complex, it is pro-inflammatory, controlling transcription of pro-inflammatory cytokines[24]. Conversely, p50 has anti-inflammatory properties in the p50 homodimer by repressing transcription[25]. The relative abundance of p65/p50 heterodimers and p50 homodimers may determine the magnitude of inflammation by balancing the pro-inflammatory and anti-inflammatory response[21]. In fact, p50 deficient mice have an increased sensitivity to lipopolysaccharide (LPS) and have increased LPS-induced inflammation[26,27]. In subjects with the del/del genotype, decreased p50 synthesis may lead to decreased repressive homodimers and increased active heterodimers of the NF-κB complex. This balance may influence the susceptibility to inflammatory diseases, including UC.

The significant association between the rs28362491 ATTG deletion allele and UC was first reported by Karban *et al*[19]. Borm *et al*[28] also reported the same results. However, several studies did not find a significant association between this allele and UC[29-32]. On the other hand, there have been no reports on the association between the *NFKB1* polymorphism and UC in Japan. In our study, the rs72696119 G allele, in linkage disequilibrium with the rs28362491 ATTG deletion allele, was significantly associated with susceptibility to UC using a recessive genetic model. In addition, this genotype was associated with patients who developed UC at a relatively young age, similar to Borm's report[28]. These contrasting observations may be explained by differences in the genotypic composition of populations in different countries with different racial groups. Another explanation is that it is possible that the results may be controlled by the composition of the phenotypes in UC cases, as our results indicated that the *NFKB1* polymorphism was more closely associated with specific phenotypes of UC. Furthermore, the influence of rs72606119 has not yet been investigated. The association between rs28362491 and rs72696119 has not been described in the HapMap project. More studies will be necessary to clarify the influence of rs76296119 on susceptibility to UC.

It is difficult to evaluate the severity of UC at any one point, because it fluctuates with clinical period and medications. Thus, we assessed the association between rs7629119 and the severity of UC, when the cases with a history of hospitalization or with a maximum of 9 or more on the UCDAI score were considered to be severe cases. Our results suggested that this genotype might be associated with UC of comparatively mild or moderate severity. Moreover, a strong significant association between the rs72696119 GG homozygote and UC was found in male subjects. It is unclear why this genotype was associated with specific phenotypes and male UC cases. UC is a multifactorial disorder with both genetic and environmental etiological factors, and is considered a complex genetic disorder predicted to involve multiple genes of relatively low penetrance[33]. In fact, Fisher *et al*[34] reported that several regions of male-specific linkage were found in the susceptibility to IBD. It may be no surprise that *NFKB1* polymorphism is more closely associated with specific phenotypes of UC. Further studies will be necessary in order to clarify how the *NFKB1* polymorphism influences susceptibility to UC.

In conclusion, the GG homozygote of rs72696119, which is located in *NFKB1* 5'-UTR and is in linkage disequilibrium with rs28362491, is significantly associated with susceptibility to UC, especially in Japanese male subjects. This genotype is associated with UC of mild or moderate severity.

## COMMENTS

### Background

The incidence of ulcerative colitis (UC) is currently rising in Japan although the pathogenesis of UC is only partially understood. Recently, variations in some genes have been associated with the development of UC.

### Research frontiers

One of the linkage regions for inflammatory bowel diseases maps to chromosome 4q. In this region, the *NFKB1*, encoding 2 subunits (p50 and p105) of nuclear factor (NF)-κB, is located (4q24). A certain genetic variation, rs72696119, has been identified at position -449 C>G in 5'-UTR of *NFKB1*. In this study, the authors demonstrate that rs72696119 GG genotype is associated with the development of UC in Japan.

### Innovations and breakthroughs

Many studies have reported the association between polymorphism rs28362491 (-94 ins/del ATTG of *NFKB1*) and various inflammatory diseases. However, these studies have not always led to the same conclusions. In addition, there have been no reports investigating an association between rs72696119 and inflammatory diseases. This is the first study to report that rs72696119 is asso-

ciated with the development of UC in Japan.

### Applications

The authors assessed how genetic variation contributes to the development of UC using a case-control study (174 cases and 465 controls). The genotype analysis was performed by polymerase chain reaction-single strand conformation polymorphism.

### Terminology

NF-κB activation is known to regulate cellular growth responses, including apoptosis, and is required for the induction of inflammatory and tissue-repair genes. NF-κB names a number of different transcription factors that are homo- or heterodimers of p65, p50, p105, C-rel and relB. Subunits p105 and p50 of NF-κB are encoded by *NFKB1*. A p65/p50 heterodimer is pro-inflammatory, and p50 has anti-inflammatory properties.

### Peer review

It is suitable for acceptance to this journal. Authors compared the GG homozygote in UC patients between total colitis and not total colitis.

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