ORIGINAL ARTICLE

No association between *TNFSF15* and *IL23R* with ulcerative colitis in Koreans

Suk-Kyun Yang¹, Yusun Jung², Myunghee Hong², Hyeri Kim², Byong Duk Ye¹, Inchul Lee³ and Kyuyoung Song²

Recent genome-wide association studies have shown that some Crohn's disease (CD)-associated loci also contribute to ulcerative colitis (UC) susceptibility. To understand the genetic relationship between the two forms of inflammatory bowel disease, we investigated the well-established CD-susceptibility genes *TNFSF15* (tumor necrosis factor ligand superfamily, member 15) and *IL23R* in Korean patients with UC. Eight *TNFSF15* and five *IL23R* single-nucleotide polymorphisms were genotyped in 654 patients with UC and in 601 healthy controls. There was no association between *TNFSF15* or *IL23R* variants and UC in Korean individuals, in contrast to previous reports of a shared association of the *IL23R* gene with both CD and UC in Caucasian individuals. Our data suggest that neither *TNFSF15* nor *IL23R* variants contribute to UC susceptibility in Koreans.

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Keywords: association; *IL23R*; Korean; *TNFSF15*; ulcerative colitis

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are the two major forms of chronic inflammatory bowel diseases (IBD) of unknown etiology. Genetic epidemiology studies have suggested that UC and CD are polygenic diseases related to each other, and that genetic susceptibility and environmental factors are involved in the pathogenesis of both the diseases.^{1–4} The incidence of IBD is relatively higher in Caucasian than in Asian populations; however, the incidence in Asia is increasing.^{5,6} Of the two types of IBD, the genetic contribution to disease risk has been documented more extensively and clearly for CD^{7–17} than for UC.^{18–21} So far, linkage and genome-wide association studies have identified more than 30 CD-susceptibility loci in Caucasian populations.²² Of those, *NOD2*, *ATG16L1* and *IRGM* were CD specific, whereas genes involved in Th17 differentiation, including *IL23R*, *IL12B*, *JAK2*, *STAT3* and *TNFSF15* were shared between UC and CD in Caucasians.^{23–26}

TNFSF15 (tumor necrosis factor ligand superfamily, member 15) was the first CD-susceptibility gene identified through a genome-wide association screening of 72 738 single-nucleotide polymorphisms (SNPs) in Japanese population.¹⁰ The association was well replicated by several studies, including our previous study in a Korean cohort,²⁷ an independent Japanese cohort²⁸ and a US cohort,²⁹ and meta-analyses of genome-wide association studies in European populations,²² although the association was less significant in Europeans than in Japanese or Korean individuals.^{29,30} However, reports of an association of *TNFSF15* with UC in Caucasians have been inconsistent.^{24–26}

In a previous report on Korean patients with CD, we replicated findings from studies on Caucasian populations, establishing inter-

leukin 23 receptor (*IL23R*) and *TNFSF15* as CD-susceptibility genes.^{27,31} Because some CD candidate genes involved in the Th17 pathway were shown to be shared with UC in Caucasians, in this study we sought to test the association between *IL23R* or *TNFSF15* polymorphisms and UC in Koreans. We found that *IL23R*, which was reported to be associated with UC as well as CD in Caucasians, was not associated with UC in Koreans. However, *TNFSF15* showed a marginal association with UC in male patients only.

SUBJECTS AND METHODS

Study subjects

The study population consisted of 654 UC patients (341 men and 313 women), 651 CD patients (442 men and 209 women) and 601 unrelated healthy controls (310 men and 291 women). Part of this cohort has been studied previously.^{27,31} All patients with UC or CD were diagnosed at the IBD Clinic of Asan Medical Center, Seoul, Korea on the basis of conventional, clinical, radiological, endoscopic and histopathological criteria.^{32,33} Patients with indeterminate colitis were excluded from the study. For controls, disease-free individuals were recruited from the Health Promotion Center of the Asan Medical Center where routine health checkups are carried out. Phenotypic subgroups of UC were determined by two independent investigators (SKY and BDY), blinded to the results of the genotype analysis, using the Montreal classification.³⁴ Briefly, phenotypes were classified on the basis of maximal endoscopic extent as E1 (ulcerative proctitis), E2 (left-sided UC) or E3 (extensive UC). The demographic and clinical characteristics of the study population are summarized in Table 1.

¹Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; ²Department of Biochemistry and Molecular Biology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea and ³Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
Correspondence: Dr K Song, Department of Biochemistry and Molecular Biology, Asan Medical Center, University of Ulsan College of Medicine, 388-1 Pungnap-Dong, Songpa-Gu, Seoul 138-736, Korea.
E-mail: kysong@amc.seoul.kr

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Table 1 Clinical characteristic of the study subjects

	UC (n=654) N (%)	CD (n=651) N (%)	Controls (n=601) N (%)
Sex			
Male	341 (52.1)	442 (67.9)	310 (51.6)
Female	313 (47.9)	209 (32.1)	291 (48.4)
Mean age at sampling (year)	40.8 ± 13.3	27.4 ± 8.1	30.7 ± 11.2
Mean age at diagnosis (year)	36.7 ± 12.9	24.3 ± 7.7	
Extent			
Proctitis	199 (30.4)		
Left-sided colitis	204 (31.2)		
Extensive colitis	251 (38.4)		

Abbreviations: CD, Crohn's disease; UC, ulcerative colitis.

Gender distributions were statistically similar in UC and control groups, but age distributions were not. This study was approved by the institutional review board of Asan Medical Center, and written informed consent was obtained from all the subjects.

SNP genotyping

Genomic DNA was isolated from 5-ml samples of EDTA-anticoagulated venous blood by standard methods, using proteinase K and phenol/chloroform extraction. Eight *TNFSF15* SNPs (rs4574921, rs10114470, rs3810936, rs6478108, rs4979462, rs7848647, rs7865494 and rs1322057) and five *IL23R* SNPs (rs1004819, rs2201841, rs10889677, rs11209032 and rs1495965) were selected for genotyping. Samples were genotyped using a matrix-assisted laser desorption/ionization time-of-flight mass spectrometry-based system (Sequenom, San Diego, CA, USA) at the Analytical Genetics Technology Centre, Princess Margaret Hospital/University Health Network in Toronto, Canada.

Statistical analysis

Genotype frequencies between cases and controls were checked separately for consistency with those expected from Hardy–Weinberg equilibrium using SNP Aylze software, version 5.0 (Dynacom, Yokohama, Japan). The associations were examined by comparing allele and genotype frequencies in different groups of subjects using a χ^2 test with permutation correction using PLINK 2.050 (<http://pngu.mgh.harvard.edu/purcell/plink/>)³⁵ and version 4.2 of the Haploview program (<http://www.broadinstitute.org/haploview/haploview>). Allelic frequencies were compared between cases and controls using logistic regression to calculate age- and gender-adjusted odds ratios and 95% confidence intervals. Genotype–phenotype analyses were performed for SNPs in cases in which the *P*-value was less than 0.2 in case–control analysis. Logistic regression analyses were also conducted to examine any significant associations between polymorphisms and disease phenotypes. The data were analyzed using SPSS version 18.0.0 for windows (SPSS, Chicago, IL, USA).

RESULTS

Association analysis of TNFSF15 and IL23R polymorphisms with UC in Koreans

Eight *TNFSF15* SNPs and five *IL23R* SNPs were genotyped in 654 UC patients and 601 healthy controls. None of the 13 SNPs showed significant deviation from the Hardy–Weinberg equilibrium.

The genotypic and allelic distributions of the 13 SNPs are summarized in Table 2. A χ^2 test of homogeneity in both allele and genotype distributions among UC patients and controls failed to show any

Table 2 Summary of association of TNFSF15 and IL23R between UC cases and controls

ID	Gene	Position ^a	Allele ^b			Genotype of case			Genotype of control			Allele 1 vs 2		Genotype 11 vs 22		Genotype 11+12 vs 22		Genotype 11 vs 12+22	
			1	2	C	11	12	22	Sum	11	12	22	Sum	χ^2 (P-value)	aOR (95% CI)	P-value	aOR (95% CI)	P-value	aOR (95% CI)
			T	C	T	C	T	C	T	C	T	C	T	T	T	T	T	T	T
rs4574921	<i>TNFSF15</i>	116578155	T	C	283 (44.9%)	289 (46.0%)	58 (9.2%)	630	238 (40.3%)	283 (47.9%)	70 (11.8%)	591	3.61 (0.057)	1.37 (0.90–2.07)	0.145	1.32 (0.89–1.97)	0.164	1.11 (0.87–1.42)	0.408
rs10114470	<i>TNFSF15</i>	116587593	C	T	174 (27.7%)	327 (52.1%)	127 (20.2%)	628	145 (24.6%)	298 (50.6%)	146 (24.8%)	589	3.57 (0.059)	1.29 (0.91–1.84)	0.152	1.29 (0.96–1.73)	0.087	1.08 (0.82–1.43)	0.577
rs3810936	<i>TNFSF15</i>	116592706	C	T	175 (27.3%)	333 (51.9%)	134 (20.9%)	642	143 (23.9%)	307 (51.3%)	149 (24.9%)	599	3.39 (0.066)	1.27 (0.90–1.81)	0.175	1.25 (0.94–1.67)	0.130	1.10 (0.83–1.45)	0.509
rs6478108	<i>TNFSF15</i>	116598524	T	C	194 (30.3%)	320 (49.5%)	132 (20.4%)	646	144 (24.0%)	315 (52.6%)	140 (23.4%)	599	4.97 (0.026)	1.33 (0.94–1.88)	0.108	1.16 (0.87–1.56)	0.314	1.26 (0.96–1.65)	0.100
rs4979462	<i>TNFSF15</i>	116606834	T	C	78 (12.3%)	301 (47.6%)	254 (40.1%)	633	63 (10.6%)	266 (44.6%)	268 (44.9%)	597	2.90 (0.089)	1.28 (0.86–1.91)	0.229	1.12 (0.88–1.43)	0.373	1.23 (0.84–1.80)	0.285
rs7848647	<i>TNFSF15</i>	116608867	C	T	199 (30.8%)	318 (49.1%)	130 (20.1%)	647	146 (24.5%)	313 (52.6%)	136 (22.9%)	595	5.02 (0.025)	1.35 (0.95–1.91)	0.095	1.16 (0.87–1.56)	0.316	1.28 (0.97–1.68)	0.076
rs7865494	<i>TNFSF15</i>	116616300	T	C	17 (2.6%)	177 (27.4%)	451 (69.9%)	645	14 (2.3%)	153 (25.5%)	432 (72.1%)	599	0.73 (0.393)	1.27 (0.59–2.76)	0.546	1.09 (0.84–1.43)	0.510	1.24 (0.58–2.69)	0.579
rs1322057	<i>TNFSF15</i>	116618195	G	A	83 (13.7%)	281 (46.4%)	242 (40.0%)	606	65 (10.9%)	267 (44.6%)	267 (44.6%)	599	3.71 (0.054)	1.35 (0.91–2.01)	0.133	1.13 (0.88–1.44)	0.345	1.31 (0.90–1.90)	0.158
rs1004819	<i>IL23R</i>	67442801	T	C	215 (35.4%)	280 (46.0%)	113 (18.6%)	608	190 (31.9%)	283 (47.6%)	122 (20.5%)	595	1.76 (0.185)	1.26 (0.89–1.78)	0.202	1.12 (0.82–1.52)	0.488	1.23 (0.95–1.60)	0.113
rs2201841	<i>IL23R</i>	67466790	C	T	351 (55.0%)	238 (37.3%)	50 (7.8%)	639	301 (51.3%)	244 (41.6%)	42 (7.2%)	587	0.69 (0.407)	0.96 (0.60–1.54)	0.863	0.89 (0.56–1.40)	0.603	1.16 (0.91–1.49)	0.220
rs10889677	<i>IL23R</i>	67497708	A	C	355 (54.4%)	247 (37.8%)	51 (7.8%)	653	300 (50.3%)	252 (42.3%)	44 (7.4%)	596	1.01 (0.315)	0.99 (0.62–1.58)	0.979	0.92 (0.58–1.44)	0.699	1.17 (0.92–1.49)	0.192
rs11209032	<i>IL23R</i>	67512680	A	G	162 (25.8%)	296 (47.2%)	169 (27.0%)	627	125 (21.3%)	294 (50.0%)	169 (28.7%)	588	2.46 (0.117)	1.38 (0.98–1.95)	0.065	1.07 (0.82–1.41)	0.624	1.43 (1.07–1.91)	0.015
rs1495965	<i>IL23R</i>	67526096	G	A	174 (26.7%)	321 (49.2%)	158 (24.2%)	653	146 (24.5%)	295 (49.5%)	155 (26.0%)	596	0.98 (0.323)	1.23 (0.87–1.72)	0.238	1.09 (0.83–1.44)	0.548	1.21 (0.92–1.59)	0.181

Abbreviations: aOR, adjusted odds ratios for age and sex; CI, confidence interval.

^aChromosome position.

^bAllele 1 is risk allele.

Table 3 Association of *TNFSF15* between IBD cases and controls

ID	Position	Risk allele			Control	RAF			Association P-value		
		IBD	UC	CD		IBD	UC	CD	IBD	UC	CD
rs4574921	116578155	T	T	T	0.642	0.740	0.679	0.802	1.1E-09	5.7E-02	1.4E-18
rs10114470	116587593	C	C	C	0.499	0.614	0.537	0.692	4.3E-11	5.9E-02	3.8E-22
rs3810936	116592706	C	C	C	0.495	0.613	0.532	0.694	7.9E-12	6.6E-02	4.9E-24
rs6478108	116598524	T	T	T	0.503	0.636	0.548	0.724	1.0E-14	2.6E-02	9.0E-30
rs4979462	116606834	T	T	T	0.328	0.456	0.361	0.551	1.4E-13	8.9E-02	9.0E-29
rs7848647	116608867	C	C	C	0.508	0.641	0.553	0.729	1.0E-14	2.5E-02	7.4E-30
rs7865494	116616300	T	T	T	0.151	0.158	0.164	0.153	5.7E-01	3.9E-01	8.9E-01
rs1322057	116618195	G	G	G	0.331	0.467	0.369	0.565	6.7E-15	5.4E-02	8.9E-31

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; RAF, risk allele frequency; UC, ulcerative colitis.

Table 4 Association of *IL23R* between IBD cases and controls

ID	Position	Risk allele			Control	RAF			Association P-value		
		IBD	UC	CD		IBD	UC	CD	IBD	UC	CD
rs1004819	67442801	T	T	T	0.557	0.589	0.584	0.594	6.8E-02	1.9E-01	6.7E-02
rs2201841	67466790	C	C	C	0.721	0.739	0.736	0.743	2.3E-01	4.1E-01	2.0E-01
rs10889677	67497708	A	A	A	0.715	0.738	0.733	0.742	1.4E-01	3.2E-01	1.2E-01
rs11209032	67512680	A	A	A	0.463	0.509	0.494	0.523	9.0E-03	1.2E-01	3.0E-03
rs1495965	67526096	G	G	G	0.492	0.521	0.512	0.529	1.1E-01	3.2E-01	6.6E-02

Abbreviations: CD, Crohn's disease; IBD, inflammatory bowel disease; RAF, risk allele frequency; UC, ulcerative colitis.

significant markers. The differences in allele frequency of the eight *TNFSF15* SNPs between controls and UC patients ranged from 1.3% for rs7865494 to 4.5% for both rs6478108 and rs7848647. However, upon association analyses by gender, a few markers from *TNFSF15* showed marginally significant association with UC in men only. Four markers showing marginally significant associations only in male UC patients include rs10114470 (5.5%, $P=0.050$), rs6478108 (7.0%, $P=0.012$), rs7848647 (6.9%, $P=0.014$) and rs1322057 (5.5%, $P=0.044$). The differences in allele frequencies of the four SNPs in women UC patients were 2.0, 1.7, 2.0 and 1.9%, respectively, and were not statistically significant. The adjusted OR for rs10114470 in men was 1.55 ($P=0.032$), for rs6478108 was 1.48 ($P=0.034$) and for rs7848647 was 1.48 ($P=0.034$). However, the significance of these results could not be confirmed using a 1000 permutation test.

A comparison of our UC data with our CD data (Table 3) showed that seven of the eight SNPs of *TNFSF15* tested, showed significant associations with CD. The differences in allele frequency of the eight *TNFSF15* SNPs between controls and CD patients ranged from 16% for rs4574921 to 23.4% for rs1322057. The adjusted odds ratio of rs1322057 for GG genotype in comparison with AA genotype was 6.91 (95% confidence interval=4.81–9.92, $P=1.5 \times 10^{-25}$) and adjusted odds ratio of rs4574921 for CC genotype in comparison with TT genotype was 4.65 (95% confidence interval=2.82–7.68, $P=1.9 \times 10^{-9}$).

In the five *IL23R* SNPs genotyped in the Korean samples, the differences in the risk allele frequency between the UC and control groups were 2.7% for rs1004819, 1.5% for rs2201841, 1.8% for rs10889677, 3.1% for rs11209032 and 2.0% for rs1495965; none of these differences were statistically significant. Following association

analyses, none of them showed significant association with UC (Table 2). However, in CD patients, the differences in the risk allele frequency between the CD and control groups were 3.7% for rs1004819, 6.0% for rs11209032 and 3.7% for rs1495965, and were statistically significant (Table 4). The three SNPs (rs1004819, rs11209032 and rs1495965) showed significant associations with CD ($P=0.003$ in a recessive model for rs1004819; $P=0.003$ in an allelic model for rs11209032; $P=0.031$ in a recessive model for rs1495965).

DISCUSSION

Recent studies have shown that genes involved in Th17 differentiation, including *IL23R*, *IL12B*, *JAK2*, *STAT3*, *CCR6* and *TNFSF15*, are associated with both CD and UC in Caucasians.^{23–26} In the present study, we investigated the well-established CD-susceptibility genes *TNFSF15* and *IL23R* in Korean UC patients.

TNFSF15 is a CD-susceptibility gene in Asians as well as in Caucasian individuals.^{10,16,27–30} In fact, the association of *TNFSF15* with CD is much stronger in Asians than in Caucasians.^{29,30} The association of *IL23R* with CD is consistently observed in Caucasians, but among Asians, this association has been demonstrated only in Koreans.³¹ Given that both *IL23R* and *TNFSF15* were suggested to be associated with UC in Caucasians,^{11,25,26,29} we sought to test the association between polymorphisms of *IL23R* and/or *TNFSF15* and UC in Koreans.

We failed to observe a significant association of *TNFSF15* polymorphisms with UC in Korean individuals, except marginal association with male UC patients. Previous reports of *TNFSF15* association with UC in Caucasians have been inconsistent,^{24–26} although they did not test identical SNPs of *TNFSF15*. Franke *et al.*²⁴ reported an

association of rs7869487 of *TNFSF15* with CD and IBD ($P=0.010$, $P=0.031$, respectively) but not with UC ($P=0.42$), whereas Wang *et al.*²⁵ reported a significant association of rs4263839 with UC ($P=8.6\times 10^{-4}$). Recently, it was reported in a genome-wide association study that rs11554257 located 39.2 kb upstream of *TNFSF15* was implicated in severe UC, as medically refractory cases were compared with healthy controls ($P<5.0\times 10^{-5}$).²⁶ Interestingly, rs7869487, which failed to show an association with UC in Caucasians, is located 12.5 kb upstream of *TNFSF15* and 2.5 kb from rs1322057, which showed the most significant association with CD ($P=1.5\times 10^{-25}$, $OR=6.91$), but not with UC, in our Korean population. rs4263839 in intron 1 of *TNFSF15* showed a significant association with UC in Caucasians, but rs4979462, 574 bp away from rs4263839, showed strong association with CD only in Koreans. Although our study was ongoing, a Japanese group reported an association of *TNFSF15* with UC and CD.³⁶ This study tested a single SNP from *TNFSF15* (rs3810936) in small groups of 82 UC patients, 130 CD patients and 163 controls, and reported positive associations with both UC and CD. However, in our study on Koreans, the difference in the frequency of this allele between controls and UC patients was only 3.7% in comparison with 11.2% in the Japanese population, and was not statistically significant. We also investigated the association of *TNFSF15* polymorphism with UC sub-phenotypes based on disease extent, but did not find any significant association between specific phenotypes and *TNFSF15* variants.

We failed to replicate an association of *IL23R* with UC in Koreans. Although none of the five *IL23R* SNPs showed a positive association with UC, rs1004819, rs11209032 and rs1495965 showed significant associations with CD in Koreans. Upon a subtype analysis of UC, a statistically marginal association was observed between left-sided colitis and *IL23R* SNPs rs10889677 ($P=0.022$ in a dominant model) and rs2201841 ($P=0.029$ in a genotypic model) (data not shown). Notably, the SNPs of *IL23R* that showed an association with CD or subtypes of UC are not overlapping. Our samples represent one of the largest IBD collections from a single institution under strict inclusion criteria. However, it is possible that our subgroup analyses are underpowered because of the limited sample size for revealing the genotype-phenotype relationship. Therefore, it is necessary to expand the number of samples of each UC subgroup for further studies. We also need to expand our study to include other genes implicated in Th17 differentiation than *TNFSF15* and *IL23R* to investigate the differential pathogenesis of UC and CD in Asians.

In summary, we report no significant association between *TNFSF15* or *IL23R* polymorphisms and UC in a Korean population.

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