# Association between NFATC2 polymorphisms and remission in rheumatoid arthritis patients receiving TNF-α inhibitors

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**Abstract**

Aim: This study aimed to examine the effects of polymorphisms in nuclear factor of activated T cells C2 (NFATC2), a TNF-α transcription factor, on remission in RA patients receiving TNF-α inhibitors. Methods: This prospective observational study was performed in two centers. Nine single nucleotide polymorphisms (SNPs) were investigated, and haplotype analyses were performed. Logistic regression analyses were used to investigate the association between genetic polymorphisms and remission of RA. Results: This study included 88 patients, among whom 26 had remission of RA. We identified a haplotype, H2 (CCT), which carried 3 NFATC2 SNPs (rs1052649, rs1569736, and rs763944) and showed a significant relationship with remission. After adjusting for covariates, H2 carriers exhibited approximately 2.86-fold higher rates of remission than others (p=0.049). In subgroup analysis with patients with the TT genotype of rs1799964 of TNF-α, patients with the CC genotype in NFATC2 rs763944 showed an approximately 4.1-fold lower remission rate than T-allele carriers (p = 0.028), after adjusting for related covariates. In another subgroup analysis among patients with the GG genotype of TNF-α rs361525, patients with the CC genotype in NFATC2 rs763944 showed an approximately 3.2-fold lower remission rate than T-allele carriers (p = 0.04) after adjusting for covariates. Conclusion: This study suggested an association between NFATC2 polymorphisms and remission in RA patients receiving TNF-α inhibitors.

**What is already known about the subject**

-Several studies have been conducted to evaluate the effects of genetic variants on the efficacy of TNF-α inhibitors and concluded that polymorphisms within immune-modulating genes may influence response to TNF-α inhibitors in RA patients.

-Nuclear factor of activated T cells C2 (NFATC2) is known as a member of the transcription family and enhance TNF-α synthesis in human T cells at the gene transcription level.

-Although NFATC2 has a potential role in RA progression and treatment, no study has investigated the association between NFATC2 gene polymorphisms and remission in RA patients receiving TNF-α inhibitors.

**What this study adds:**

-This is the first study to investigate the effects of genetic variations in the NFATC2 gene on remission rate of RA in patients taking TNF-α inhibitors.

-There is an association between NFATC2 polymorphisms and remission in RA patients receiving TNF-α inhibitors.

-Patients taking sulfasalazine with TNF-α inhibitors showed higher remission rates than patients not taking sulfasalazine.

## Introduction

Rheumatoid arthritis (RA) is an autoimmune disease that affects about 24.5 million people worldwide [1]. It is characterized by a chronic inflammatory reaction in the synovium of joints. Several factors have been reported to cause RA, including smoking, obesity, and vitamin D deficiency. In addition, a genetic component has been suggested to be a strong factor for RA. Twin studies have shown that the heritability of RA is approximately 60% [2]. The involvement of many genes in RA has been studied, and most of these genes are related to the immune system. The most well-known genetic risk factors for RA are variations in human leukocyte antigen (HLA) genes, especially the HLA-DRB1 gene [3].

Tumor necrosis factor alpha (TNF-α) inhibitors are commonly used in patients with high disease activity [4]. TNF-α inhibitors bind to TNF-α, a pro-inflammatory cytokine involved in RA pathology [5] and inhibit its interaction with TNF receptors [6]. Five TNF-α inhibitors are available for RA therapy: adalimumab, certolizumab, etanercept, golimumab, and infliximab. Although TNF-α inhibitors are widely used, only two-thirds of RA patients respond to the treatment [7]. Several studies have been conducted to evaluate the effects of genetic variants on the efficacy of TNF-α inhibitors. One showed that TNF levels were elevated due to polymorphisms resulted in RA [8], while another showed that RA patients with a certain genotype were more responsive to TNF-α inhibitors than those with other genotypes [9]. Furthermore, a case-control study concluded that polymorphisms within immune-modulating genes may influence response to TNF-α inhibitors in RA patients [10].

Nuclear factor of activated T cells C2 (NFATC2) is known as a member of the transcription family, and ectopic expression of NFATC2 is known to enhance TNF-α synthesis in human T cells at the gene transcription level [11]. Since NFATC2 is a transcription factor of TNF-α, impaired function of NFATC2 could affect RA treatment. Although NFATC2 has a potential role in RA progression and treatment, no study has investigated the association between NFATC2 gene polymorphisms and remission in RA patients receiving TNF-α inhibitors.

Therefore, this study aimed to examine the association between NFATC2 polymorphisms and remission in RA patients receiving TNF-α inhibitors.

## Methods

### Study patients

A total of 105 patients who received TNF-α inhibitors (adalimumab, etanercept, golimumab or infliximab) between July 2017 and December 2019 were recruited from Ajou University Hospital and Chungbuk National University Hospital. Data on sex, age, weight, height, duration of RA, alcohol consumption, smoking, autoantibodies against rheumatoid factor, anti-cyclic citrullinated peptide, concomitant drugs, and comorbidities were collected from electronic medical records. Additionally, baseline data of disease activity score (DAS)-28 and its subcomponents, which included swollen joint count (SJC)-28, tender joint count (TJC)-28, global health (GH), and erythrocyte sedimentation rate (ESR) or C-reactive protein levels, were collected.

DAS-28 was calculated as 0.56 × [?](TJC28) + 0.28 x [?](SJC28) + 0.70 x ln(ESR) + 0.014 x GH [12]. Remission from RA was defined as DAS-28< 2.6 after 6 months of treatment [12].

This prospective observational study was approved by the Institutional Review Board of the Ajou University Hospital (approval number: AJIRB-BMR-OBS-17-153) and Chungbuk National University Hospital (approval number: 2017-06-011-004). All patients submitted written informed consents for participation. This study was conducted according to the principles of the Declaration of Helsinki (2013).

### Genotyping methods

To select single nucleotide polymorphisms (SNP) of NFATC2 that might be associated with RA remission,

genetic information on NFATC2 was obtained from the PharmGKB database, Haploreg 4.1, Database of SNPs (dbSNP) from NCBI, and previous studies [13-17]. Seven SNPs of NFATC2 (rs763944, rs1569736, rs4811191, rs2426295, rs3787186, rs6013193, and rs1052649) were selected. In addition to the selected SNPs, TNF-α rs1799964 and rs361525, which are known to have significant effects on treatment of RA, were also included in the study [18]. Thus, a total of nine SNPs was investigated.

Genomic DNA of the patients was isolated from ethylenediaminetetraacetic acid–blood samples using the QIAamp DNA Blood Mini Kit (Qiagen GmbH, Hilden, Germany) according to the manufacturer's protocol. Genotyping was performed using a single-base primer extension assay with SNaPShot multiplex kits (ABI, Foster City, CA, USA) or TaqMan genotyping assay in a real-time PCR system (ABI 7300, ABI), according to the manufacturer's recommendations.

**Statistical analysis**

Student's $t$ -test was utilized to compare continuous variables between patients who reached remission and who did not. Chi-square test or Fisher's exact test was used to compare categorical variables between the two groups. LD (D') between two loci in a gene was calculated using Haploview 4.2 [19], and haplotype analysis was performed using Plink [20]. Multivariable logistic regression analysis was used to examine independent factors for remission; factors having a $p$- value less than 0.15 in univariate analysis along with clinically relevant confounders were included in multivariable analysis. The Hosmer-Lemeshow test was performed to confirm the model's goodness of fit. Genotype-Tissue Expression (GTEx) Portal was used to determine the expression profile of the NFATC2 gene [21]. Statistical significance was considered at $p$- values of less than 0.05. All statistical analyses were conducted using IBM SPSS statistics, version 20 software (International Business Machines Corp., New York, NY, USA).

**Results**

Among the 105 patients enrolled in this study, 17 patients were excluded due to the incompleteness in medical data; consequently, data from 88 patients taking TNF-α inhibitors were analyzed.

The mean age of the included patients was 44 years (range: 20–78 years), and there were 72 (81.8%) females. The mean duration of RA was 8.6 years. As shown in Table 1, methotrexate was the most common concomitant drug administered (70.5%), followed by hydroxychloroquine (55.7%). Prescription of sulfasalazine and TNF-α inhibitors more likely resulted in remission than prescription of TNF-α inhibitors without sulfasalazine ($p = 0.036$). There was no significant difference in comorbidities between the two groups. The most prevalent comorbidity was hypertension (15.9%), followed by hyperlipidemia and osteoporosis (both 11.4%).

Baseline DAS28 and its subcomponents were examined to determine the possible influence of disease status of patients on their response to TNF-α inhibitors. There was no significant difference in baseline DAS28 or its subcomponents between the groups with and without remission (Table 1).

The effects of genotypes on remission are shown in Table 2. Although a statistically significant association was not found between the studied SNPs and remission, rs763944 showed marginal significance; remission in T-allele carriers was almost twice that in variant-type homozygous carriers.

Since three of the NFATC2 polymorphisms analyzed in this study were in strong LD (D' range: 0.94–1.00), we constructed a haplotype of the NFATC2 gene with rs1052649, rs1569736, and rs763944. Four haplotypes were detected at frequencies of more than 1%: H1 (TCC, 41.5%, $p = 0.125$), H2 (CCT, 30.7%, $p = 0.070$), H3 (CAC, 26.1%, $p = 0.878$), and H4 (TCT, 1.1%, $p = 0.359$). The haplotype with the lowest $p$- value was H2, which contained wild-type alleles at every locus; H2 carriers had more frequent remission than those without H2 ($p = 0.043$).

We performed multivariable logistic regression analysis to determine independent factors, which included both genetic and non-genetic variables. Age, BMI, and factors with $p$ -values less than 0.15 in the univariate analysis were included. After adjusting for related covariates, H2 carriers were revealed to have an approxi-

mately 2.9-fold higher rate of remission than others (Table 3). The Hosmer–Lemeshow test showed that the fitness was satisfactory ($\chi^2 = 6.995$, 6 degrees of freedom, $p = 0.321$).

To rule out the effect of TNF-α, subgroup analyses were performed. In subgroup analysis using patients with the TT genotype of TNF-α rs1799964, age, BMI, and factors with $p$- values less than 0.15 in the univariate analysis (sex, hypertension, rs1052649 and rs763944, and sulfasalazine) were included (Table 4). After adjusting for related covariates, patients with the CC genotype in rs763944 showed an approximately 4.1-fold lower remission rate than T-allele carriers ($p = 0.028$). In addition, patients who were taking sulfasalazine concurrently with TNF-α inhibitors had an about 6.4-fold higher remission rate than those who were not taking sulfasalazine ($p= 0.031$). The Hosmer–Lemeshow test showed satisfactory fitness ($\chi^2 = 0.653$, 1 degree of freedom, $p = 0.419$).

In another subgroup analysis using patients with the GG genotype of TNF-α rs361525 (Table 5), patients with the CC genotype in NFATC2 rs763944 showed approximately 3.2-fold lower remission rate than T-allele carriers after adjusting for covariates ($p = 0.04$). After adjusting for related covariates, patients who were taking sulfasalazine concurrently with TNF-α inhibitors had an about 5.0-fold higher remission rate than those who were not taking sulfasalazine ($p = 0.026$). The Hosmer–Lemeshow test showed that the fitness was satisfactory ($\chi^2 =1.111$, 3 degrees of freedom,$p = 0.774$).

To verify the effects of chosen SNPs on NFATC2 gene expression, we performed eQTL analysis of the NFATC2 expression profile using the GTEx Portal database. Among three SNPs used in haplotype analysis, two (rs1052649 and rs1569736) were not found in the GTEx datasets. Rs763944 was recorded as a significant expression quantitative trait locus with the NFATC2 transcript ($p = 5.2 \times 10^{-6}$) [21], resulting in higher expression with variant-type alleles in esophageal mucosa.

**Discussion**

The main finding of the present study is that the NFATC2 haplotype H2 (CCT), which carries 3 SNPs (rs1052649, rs1569736, and rs763944, respectively), was associated with remission from RA among patients who received TNF-α inhibitor therapy. H2 carriers experienced a 2.89-fold higher rate of remission than others. In addition, subgroup analyses showed that rs763944 and sulfasalazine were significantly correlated with remission rate in patients who underwent TNF-α inhibitor treatment.

The NFAT family of transcription factors is associated with T lymphocytes and is known to be involved in cell cycle, apoptosis, angiogenesis, and metastasis [22-26]. NFATC2, also known as NFAT1, is one of the five members of the NFAT family. It is located on human chromosome 20 and plays a central role in inducing gene transcription during the immune response [14]. In clinical settings, nuclear translocation of NFATC2 showed increased cytokine production and thus subsequent tissue and organ damage in systemic lupus erythematosus patients [27]. Another study on AIDS patients with immune reconstitution inflammatory syndrome (IRIS) showed that increased NFATC2 levels promote the expression of TNF-?, thereby increasing the occurrence of IRIS [28]. In consideration of these findings, NFATC2 gene plays an important role in clinical outcomes.

Four putative NFAT-binding sites have been reported in the TNF-α promoter [29-32]. Among them, NFATC2 binds to all the elements in the TNF-α promoter [29] and induces TNF-α transcription effectively owing to a long transcriptional activation domain that increases TNF-α promoter transactivation [11]. Accordingly, NFATC2 affects the function of TNF-α· NFATC2 knockdown cells show a reduction of TNF-α-induced CX3CL1 and VCAM1 expression by 45.6% and 34.9%, respectively [33].

CX3CL1 and VCAM1 play a crucial role in the pathogenesis of RA and in TNF-α inhibitor treatment. A study showed that patients who were treated with infliximab showed a decline in CX3CL1 levels. In addition, active-RA patients who did not show a clinical response to infliximab had higher basal CX3CL1 levels than patients who did [34]. Similarly, serum VCAM1 level is also associated with changes in disease condition and affects treatment in RA patients [35].

The TNF-α gene is located on human chromosome 6 and consists of four exons and three introns [36]. TNF-α regulates cell proliferation, survival, differentiation, and apoptosis [37-39]. Abnormal production and

signaling of TNF-α results in pathogenesis of several diseases including RA. Moreover, TNF-α is known as a master-regulator of inflammatory cytokine production; hence, it has an important effect in RA [40]. TNF-α inhibitors are widely used for inflammatory diseases such as RA.

Rs1799964 and rs361525 are well-known polymorphisms in TNF-α, and several studies have shown their association with immune diseases [41-43]. Although these two polymorphisms did not have significant association with remission in our study population, we carried out subgroup analyses using TNF-α wild-type homozygous carriers to rule out the possible influence of TNF- α. We found that carriers of the CC genotype at rs763944 had a significantly lower remission rate than others, whereas sulfasalazine significantly increased remission rates in subgroup analyses using patients with wild-type homozygotes of TNF-α rs1799964 and rs361525. Although rs763944 is rarely studied, it was speculated that NFATC2 rs763944 might alter transcriptional activity and function of TNF-α, thereby affecting RA disease activity. eQTL analysis performed using GTEx supported our results; rs763944 had significant eQTL association, suggesting its functional role. Rs763944 was recorded as a significant expression quantitative trait locus with the NFATC2 transcript ($p = 5.2 \times 10^{-6}$) [21], showing higher expression with variant-type alleles. Our results suggest that carriers of the CC genotype of rs763944 have a significantly lower in remission rate than others. When rs763944 in the NFATC2 gene was analyzed together with rs1052649 and rs1569736, it also showed a significant effect on remission rate. Sulfasalazine was significantly associated with remission rate in subgroup analyses. As sulfasalazine is a disease-modifying anti-rheumatic drug that reduces pain and swelling, combination therapy of TNF-α inhibitor (etanercept) and sulfasalazine results in significantly greater improvements in RA disease activity, as assessed by the DAS and physical function, than sulfasalazine alone [44]. Our findings suggest sulfasalazine as a good candidate for combination therapy with TNF-α inhibitors in RA treatment.

This study was limited by its small sample size due to the nature of RA patients in an epidemic aspect. Moreover, we did not clarify the exact mechanisms at a molecular level. However, to our knowledge, this is the first study to investigate the effects of genetic variations in the NFATC2 gene on remission rate of RA in patients taking TNF-α inhibitors. Results of this study could serve as preliminary data to develop and implement individually designed treatment to lead patients with RA to optimal outcomes.

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**Disclosure statement**

The authors declare no conflicts of interest.

**Data availability**

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Table 1. Patient characteristics according to the remission at 6 months treatment of TNF inhibitors

| Characteristics, n (%) | Remission | No remission | *p*-value |
|---|---|---|---|
| SEX | | | 0.068 |
| Male | 8 (30.8) | 8 (12.9) | |
| Female | 18 (69.2) | 54 (87.1) | |
| Age | 52.7±13.0 | 52.9±14.0 | |
| <65 | 23 (88.5) | 47 (75.8) | 0.179?¿? |
| 65 | 3 (11.5) | 15 (24.2) | |
| BMI, kg/m$^2$ | 22.8±2.6 | 22.7±3.9 | 0.855 |
| <23 | 13 (50.0) | 35 (56.5) | 0.579?¿? |
| 23 | 13 (50.0) | 27 (43.5) | |
| Duration of rheumatoid arthritis, years | 8.5±7.4 | 8.6±5.6 | 0.485 |
| Alcohol | | | 0.939 |
| Yes | 3 (12.5) | 8 (13.1) | |
| No | 21 (87.5) | 53 (86.9) | |
| Smoking | | | 0.875 |
| Yes | 3 (12.5) | 7 (11.3) | |
| No | 21 (87.5) | 55 (88.7) | |
| Rheumatoid factor | | | 0.302 |
| Positive | 2 (7.7) | 0 (0) | |
| Negative | 8 (30.8) | 15 (24.2) | |
| ACPA | | | 0.518 |
| Positive | 16 (69.6) | 43 (75.4) | |
| Negative | 7 (30.4) | 14 (24.6) | |
| Concomitant drug | | | |
| Hydroxychloroquine | | | 0.822 |
| Yes | 14 (53.8) | 35 (56.5) | |
| No | 12 (46.2) | 27 (43.5) | |
| Leflunomide | | | 0.871 |
| Yes | 10 (38.5) | 25 (40.3) | |
| No | 16 (61.5) | 37 (59.7) | |
| Methotrexate | | | 0.235 |
| Yes | 16 (61.5) | 46 (74.2) | |
| No | 10 (38.5) | 16 (25.8) | |
| Sulfasalazine | | | 0.036 |
| Yes | 7 (26.9) | 5 (8.1) | |
| No | 19 (73.1) | 57 (91.9) | |
| Tacrolimus | | | 0.747 |
| Yes | 3 (11.5) | 10 (16.1) | |
| No | 23 (88.5) | 52 (83.9) | |
| Comorbidity | | | |
| Diabetes | | | 0.665 |
| Yes | 1 (3.8) | 5 (8.1) | |

| Characteristics, n (%) | Remission | No remission | *p*-value |
|---|---|---|---|
| No | 25 (96.2) | 57 (91.9) | |
| Dyslipidemia | | | 1.000 |
| Yes | 3 (11.5) | 7 (11.3) | |
| No | 23 (88.5) | 55 (88.7) | |
| Hypertension | | | 0.057 |
| Yes | 1 (3.8) | 13 (21.0) | |
| No | 25 (96.2) | 49 (79.0) | |
| Osteoporosis | | | 0.473 |
| Yes | 4 (15.4) | 6 (9.7) | |
| No | 22 (84.6) | 56 (90.3) | |
| Vitamin D deficiency | | | 0.440 |
| Yes | 1 (3.8) | 6 (9.7) | |
| No | 25 (96.2) | 56 (90.3) | |
| Baseline DAS28 with its subcomponents | Baseline DAS28 with its subcomponents | | |
| DAS28 | 5.4±1.2 | 6.0±1.1 | 0.054 |
| Tender joint count 28 | 8.7±9.0 | 11.3±7.1 | 0.151 |
| Swollen joint count 28 | 6.0±7.8 | 7.9±5.6 | 0.216 |
| Global health | 57.1±21.0 | 60.0±17.2 | 0.528 |
| ESR | 48.5±26.5 | 51.4±28.6 | 0.655 |
| CRP | 2.0±2.1 | 2.4±3.4 | 0.575 |

BMI: body mass index; ACPA: anticyclic citrullinated peptide antibody

DAS28: disease activity score 28 joints; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein

Table 2. Genotype association with the remission at 6 months treatment of TNF inhibitors

| Gene, rs number | Remission | No remission | *p*-value |
|---|---|---|---|
| NFATC2 rs763944 | | | 0.073 |
| TT, CT | 18 (69.2) | 30 (48.4) | |
| CC | 8 (30.8) | 32 (51.6) | |
| NFATC2 rs1569736 | | | 0.689 |
| CC, AC | 23 (88.5) | 57 (91.9) | |
| AA | 3 (11.5) | 5 (8.1) | |
| NFATC2 rs4811191 | | | 0.440 |
| GG, GA | 25 (96.2) | 56 (90.3) | |
| AA | 1 (3.8) | 6 (9.7) | |
| NFATC2 rs2426295 | | | 0.515 |
| AA | 21 (80.8) | 54 (87.1) | |
| AC, CC | 5 (19.2) | 8 (12.9) | |
| NFATC2 rs3787186 | | | 0.445 |
| TT | 4 (15.4) | 14 (22.6) | |
| CT, CC | 22 (84.6) | 48 (77.4) | |
| NFATC2 rs6013193 | | | 0.747 |
| TT, GT | 23 (88.5) | 52 (83.9) | |
| GG | 3 (11.5) | 10 (16.1) | |
| NFATC2 rs1052649 | | | 0.105 |
| CC, CT | 23 (88.5) | 45 (72.6) | |
| TT | 3 (11.5) | 17 (27.4) | |
| TNF-α rs1799964 | | | 0.962 |

| Gene, rs number | Remission | No remission | $p$-value |
|---|---|---|---|
| TT | 19 (73.1) | 45 (72.6) | |
| CT, CC | 7 (26.9) | 17 (27.4) | |
| TNF-α rs361525 | | | 1.000 |
| GG | 24 (92.3) | 58 (93.5) | |
| AG, AA | 2 (7.7) | 4 (6.5) | |

NFATC2: nuclear factor of activated T cells 2; TNF-α: tumor necrosis factor-α

Table 3. Multivariate analysis to identify predictors for the remission at 6 months treatment of TNF inhibitors

| | Crude OR (95% CI) | $p$-value | Adjusted OR[b] (95% CI) | $p$-value |
|---|---|---|---|---|
| Age>[?]65 | 0.41 (0.107-1.555) | 0.189 | | |
| BMI[?]23 | 1.30 (0.518-3.247) | 0.580 | | |
| Baseline DAS28 | 0.66 (0.433-1.015) | 0.059 | | |
| Female | 0.33 (0.109-1.017) | 0.054 | 0.31 (0.090-1.061) | 0.062 |
| Hypertension | 0.15 (0.019-1.219) | 0.076 | 0.18 (0.021-1.575) | 0.121 |
| Sulfasalazine | 4.20 (1.192-14.801) | 0.026 | 3.71 (0.962-14.326) | 0.057 |
| NFATC2 H2 Carrier[a] | 2.73 (1.034-7.218) | 0.043 | 2.89 (1.00-8.35) | 0.049 |

a. H2 carrier (C carriers of rs1052649-C carriers of rs1569736-T carriers of rs763944)

b. Adjusted for Age, BMI, baseline DAS28, sex, hypertension, sulfasalazine and NFATC2 H2 carrier.

BMI: body mass index; DAS28: disease activity score 28 joints; OR: odds ratio; CI: confidence interval

Table 4. Subgroup analysis in patients with TT genotype of rs1799964

| | OR (95% CI) | $p$-value | Adjusted OR[a] (95% CI) | $p$-value |
|---|---|---|---|---|
| Age[?]65 | 0.41 (0.107-1.572) | 0.193 | | |
| BMI[?]23 | 1.15 (0.443-2.975) | 0.776 | | |
| Female | 0.39 (0.123-1.232) | 0.108 | | |
| TT genotype in rs1052649 | 0.35 (0.091-1.310) | 0.118 | | |
| CC genotype in rs763944 | 0.34 (0.121-0.929) | 0.036 | 0.32 (0.105-0.950) | 0.04 |
| Hypertension | 0.15 (0.019-1.223) | 0.076 | 0.21 (0.025-1.791) | 0.154 |
| Sulfasalazine | 5.56 (1.450-21.314) | 0.012 | 5.03 (1.210-20.953) | 0.026 |

a. Adjusted for Age, BMI, sex, hypertension, sulfasalazine rs1052649 and rs763944.

BMI: body mass index; OR: odds ratio; CI: confidence interval

Table 5. Subgroup analysis in patients with GG genotype of rs361525

| | OR (95% CI) | $p$-value | Adjusted OR[a] (95% CI) | $p$-value |
|---|---|---|---|---|
| Age[?]65 | 0.41 (0.107-1.572) | 0.193 | | |
| BMI[?]23 | 1.15 (0.443-2.975) | 0.776 | | |
| Female | 0.39 (0.123-1.232) | 0.108 | | |
| TT genotype in rs1052649 | 0.35 (0.091-1.310) | 0.118 | | |
| CC genotype in rs763944 | 0.34 (0.121-0.929) | 0.036 | 0.32 (0.105-0.950) | 0.04 |

| | OR (95% CI) | $p$-value | Adjusted OR[a] (95% CI) | $p$-value |
|---|---|---|---|---|
| Hypertension | 0.15 (0.019-1.223) | 0.076 | 0.21 (0.025-1.791) | 0.154 |
| Sulfasalazine | 5.56 (1.450-21.314) | 0.012 | 5.03 (1.210-20.953) | 0.026 |

a. Adjusted for Age, BMI, sex, hypertension, sulfasalazine rs1052649 and rs763944.

BMI: body mass index; OR: odds ratio; CI: confidence interval