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# The ITGAV-rs3911238 Polymorphism Is Associated with Disease Activity in Rheumatoid Arthritis

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## ABSTRACT

Evidences indicate that angiogenesis is an important process in the development of destructive synovial tissue in rheumatoid arthritis (RA). Recently, it has been shown that the polymorphism of the integrin-αv subunit encoded by the ITGAV gene plays a role in angiogenesis and is considered as RA susceptibility loci.

This study investigated association of four single nucleotide polymorphisms (SNPs) in ITGAV with disease activity score (DAS28), serum levels of C-reactive protein (CRP), and anti-cyclic citrullinated peptide(anti-CCP) antibody in 419 RA patients and 398 healthy individuals. Four SNPs in ITGAV gene (rs3911238, rs3738919, rs10174098 and rs3768777) were analyzed. Serum concentrations of anti-CCP antibody and CRP were measured by ELISA. We used the EULAR activity criteria to calculate DAS28-CRP.

Among these SNPs, the ITGAV-rs3911238-G/C polymorphism was associated with RA disease activity [remission-to-low and moderate-to-high in codominant model (CC vs.GG: OR=1.53, $p$=0.041 and allele (C vs. G: OR=1.18, $p$=0.042)] and presence of anti-CCP (codominant CC vs.GG: OR=2.77, $p$=0.001, allele C vs. G: OR=1.19,$p$=0.033). The carriers of CC genotype ITGAV-rs3911238 had higher serum levels of CRP and anti-CCP antibody titer and higher ESR and disease activity score than carriers of GG and CG genotypes. Furthermore, haplotypes analysis showed that ITGAV rs3733891C/rs3768777T/rs3911238C/rs10174098A and ITGAV rs3733891A/rs3768777T/rs3911238G/rs10174098A haplotypes increased severity and anti-CCP antibody in RA patients (OR=5.54, p=0.049 and OR=2.89; $p$=0.024, respectively) in comparison with ITGAV rs3733891C/rs3768777T/rs3911238G/rs10174098A haplotypes.

Thus, the present study demonstrated that the link between systemic inflammatory markers and the ITGAV-rs3911238 polymorphism allele in Iranian RA patients.

**Keywords**: Anti-CCP antibody; Disease activity score-28; ITGAV; Rheumatoid arthritis; ITGAV rs3911238

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## INTRODUCTION

Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammation of synovial tissues with massive influx of highly proliferative and invasive synovial fibroblasts and macrophages that adhere to extracellular matrix.[1] Angiogenesis plays a pivotal role in panus formation and bone and cartilage destruction in RA patients.[2] The matrix metalloproteinases secreted by the synovial fibroblasts and macrophages destroy cartilage and bone leading to deformities and disabilities.[3] In addition, stimulation of these cells by inflammatory cytokines and chemokines like interleukin(IL)-6 and IL-8 generated via integrin mediated signaling contributes significantly to progression of the disease.[4,5]

Integrins are a large group of transmembrane proteins that anchor the cell to the extracellular matrix (ECM) or other cells.[6] The integrin family is composed of at least 24 different αβ heterodimeric members among which heterodimer alphaV beta 3 (αvβ3), a receptor for ECM components such as vitronectin and fibronectin plays a major role in osteoclast-mediated bone resorption,[7-11] angiogenesis,[5,12] and macrophage dependant inflammation.[11] Integrin αvβ3 is expressed by all the cells in the synovial tissues and polymorphisms of the integrin αv subunit (ITGAV, encoding the αv chain) are associated with RA and the progression of the disease in a European Caucasian population.[13] As a key player in angiogenesis,[5] it has been suggested that ITGAV may be a RA susceptibility gene.[14,15] In animal models of arthritis, αvβ3 antagonists inhibit angiogenesis and joint inflammation.[16,17] Based on these facts, ITGAV could be involved in RA pathogenesis and study of its role may lead to novel therapeutic options.

The objective of the current work was to determine the relation of ITGAV-rs3911238, rs3738919, rs10174098, and rs3768777 alleles with the risk, disease activity of RA, and the inflammatory markers in Iranian RA patients. This is a novel and enlightening study because to the best of our knowledge, there are no other reports in the literature addressing the relation of ITGAV-rs3911238, rs3738919, rs10174098, or rs3768777 polymorphism with inflammatory markers such as anti-CCP antibodies, C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), and disease activity in RA patients.

## MATERIALS AND METHODS

### Patients

419 known and treated RA patients (375 females and 43 males) diagnosed based on 1987 ACR classification criteria were enrolled in the study. We selected 397 age and sex matched healthy individuals (363 female and 36 males) with no history of autoimmune diseases as control group. All patients and controls were informed about the study and written consent was obtained from all of them. Baseline information including demographic and age of disease onset were collected by interviewing all the participants. For calculation of disease activity score of 28 joints (DAS28-CRP), we used the EULAR activity criteria. remission was defined as DAS-28<2.6, low activity as DAS-28 between 2.6 to 3.2, moderate activity as 3.2 to 5.1 and high activity as values over 5.1.[1] All patients were under treatment with corticosteroids and methotrexate. Patients receiving other interfering drugs including therapeutic monoclonal antibodies (anti-TNF or anti-CD20) were excluded from the study.

### Anti-CCP Antibody, CRP and ESR Determination

Blood samples obtained from all participants. Serum samples were obtained by centrifugation and stored at -80°C until use. One hour ESR was determined by the westergreen method. The serum CRP titer (hs-CRP) was determined by a commercial Elisa kit (monobine Inc, USA) according to manufacture protocol. Anti-CCP antibody was assayed using a second generation kit (Genesis Diagnostics, UK).The anti-CCP level≥6.25 RU/ml was considered as threshold for a positive result.

### Genotyping

Genomic DNA was extracted from peripheral blood leukocytes using phenol chloroform extraction method.[2] Genotyping of all individuals was done without knowledge of their groups or disease. Genotyping of ITGAV rs3911238, rs3738919, rs10174098 and rs3768777 were performed using the TaqMan allelic discrimination assay as previously described.[3] All primer/probes and also master mix were from Applied Biosystems (Applied Biosystems, Foster City, CA, USA). The PCR was performed according to the manufactures recommendations. Briefly, each PCR reaction contained 100 ng DNA, 12.5 µl TaqMan

genotyping master mix, 0.6 µl of predesigned primers and probes in a total volume of 25 µl. The PCR cycles were: 50 °C for 2 minutes, 95 °C for 10 minutes, followed by 45 cycles of 95 °C for 15 seconds and 60 °C for 1 minute. PCR was performed using 96 well plates on ABI StepOnePlus instrument. The results of alleles and genotypes were determined using StepOne software V2.1 (Applied Biosystems, Foster City, CA, USA).

**Statistical Analysis**

The genotypes and alleles frequencies of ITGAV SNPs in RA patients were compared to control group and also compared between RA patients with different disease activity score (remission-to-low and moderate-to-high) using $\chi 2$ test. Odds ratios (OR) were calculated as estimates of relative risk for disease and 95% confidence intervals obtained by SPSS logistic regression. The correlation between inflammatory parameters and ITGAV SNP polymorphisms was calculated using linear regression and an unpaired t test. A two-tailed Student's t test, ANOVA, and nonparametric independent sample Mann-Whitney analyses were used to compare quantitative data. Haplotypes analysis of ITGAV (ITGAV-rs3911238, rs3733891, rs3768777, and rs10174098) genes polymorphisms in the study subjects was performed by SNPSTATS software (http://bioinfo.iconcologia.net/snpstats/start.htm). Statistical significance was assumed at the $p<0.05$.

## RESULTS

RA patients were divided into two groups based on their disease activity score: remission-to-low activity (DAS28-CRP values 0 to 3.2) and moderate-to-high activity (DAS28-CRP from 3.2 and more than 3.2) or based on the presence or lack of anti-CCP antibody in their serum. Comparison of clinical, laboratory features, and risk factors in subgroups of RA patients are demonstrated in Table 1. As expected, RA patients with moderate-high disease activity showed significantly higher CRP, ESR, number of tender and swollen joints compared with the patients with remission-low RA activity. RA patients with positive anti-CCP antibody showed significantly higher level of CRP and increased number of swollen joints than those patients who did not have anti-CCP antibody in their serum.

**Table 1. Comparison of risk factors and inflammatory markers between RA patients with different disease activity and with or without anti-CCP antibody**

| Variables | RA patients with remission and low activity (n=300) | RA patients with moderate and high activity (n=119) | RA patients with positive anti-CCP (n=193) | RA patients with negative anti-CCP (n=199) |
|---|---|---|---|---|
| Age (years) | 49.2±12.1 | 51.5±12.7 | 49.9±11.8 | 49.8±12.8 |
| | $p$=0.08 | | $p$=0.93 | |
| Sex (F/M) | 268/31 | 108/12 | 193/27 | 183/16 |
| | $p$=0.73 | | $p$=0.11 | |
| Number of tender joints | 0.947 ± 1.73 | 4.69 ± 3.4 | 2.26 ± 3.26 | 1.73 ± 2.37 |
| | $p$<0.001 | | $p$=0.062 | |
| Number of swollen joints | 0.258± 0.834 | 1.966 ± 2.167 | 0.95 ± 1.87 | 0.52 ± 1.11 |
| | $p$<0.001 | | $p$=0.002 | |
| ESR (mm/h) | 16.24 ± 13.6 | 24.18 ± 19.5 | 19.53 ± 16.9 | 17.35 ± 14.69 |
| | $p$<0.001 | | $p$=0.16 | |
| CRP (mg/L) | 4.2 ± 5.5 | 10.29 ±8.9 | 6.75 ± 8.15 | 5.1 ± 5.9 |
| | $p$<0.001 | | $p$=0.027 | |
| Anti-CCP (RU/mL) | 40.2 ± 73.5 | 43.6 ± 66 | 76.9 ± 83.9 | 1.75 ± 1.77 |
| | $p$=0.6 | | $p$<0.001 | |
| Disease duration (Years) | 9.8±6.8 | 10.5±6 | 10.2±6.6 | 9.8±6.5 |
| | $p$=0.39 | | $p$=0.37 | |
| DAS28-CRP | 2.12 ± 0.75 | 3.83 ± 0.98 | 2.68 ± 122 | 2.52 ± 1 |
| | $p$<0.001 | | $p$=0.17 | |

**Table 2. Distributions of genotypes and alleles of four SNPs in ITGAV gene between RA patients and control subjects**

| Genotypes and allele | RA patients (n=419) | Control subjects (n=397) | |
|---|---|---|---|
| ITGAV rs3911238 genotypes | | | $\chi2$=3.17, $p$=0.2 |
| G/G | 239 (57%) | 202 (50.9%) | |
| G/C | 153 (36.5%) | 166 (41.6%) | |
| C/C | 27 (6.5%) | 29 (7.6%) | |
| ITGAV rs3738919 genotypes | | | $\chi2$=1.2, $p$=0.55 |
| C/C | 158 (37.8%) | 156 (40.1%) | |
| C/A | 198 (47.4%) | 185 (47.6%) | |
| A/A | 62 (14.8%) | 48 (12.3%) | |
| ITGAV rs3768777 genotypes | | | $\chi2$=1.72, $p$=0.42 |
| G/G | 191 (45.7%) | 171 (44%) | |
| G/A | 168 (40.2%) | 172 (44.2%) | |
| A/A | 59 (14.1%) | 46 (11.8%) | |
| ITGAV rs10174098 genotypes | | | $\chi2$=2.9, $p$=0.23 |
| A/A | 189 (45.5%) | 171 (43.8%) | |
| A/G | 168 (40.5%) | 177 (45.4%) | |
| G/G | 58 (14%) | 42 (10.8%) | |
| ITGAV rs3911238 alleles | | | ($\chi2$=2.8, $p$=0.096) |
| G | 631 (75.3%) | 570 (71.8%) | |
| C | 207 (24.7%) | 224 (28.2%) | |
| ITGAV rs3733891 alleles | | | ($\chi2$=1.1, $p$=0.29) |
| C | 514 (61.5%) | 498 (64%) | |
| A | 322 (38.5%) | 280 (36%) | |
| ITGAV rs3768777 alleles | | | ($\chi2$=0.02, $p$=0.9) |
| G | 550 (65.8%) | 514 (66.1%) | |
| T | 286 (34.2%) | 264 (33.9%) | |
| ITGAV rs10174098 alleles | | | ($\chi2$=0.1, $p$=0.75) |
| A | 548 (65.8%) | 519 (66.5%) | |
| G | 284 (34.2%) | 261 (33.5%) | |

The distribution of ITGAV (ITGAV rs3911238, rs3733891, rs3768777, and rs10174098) genotypes did not deviate from the Hardy–Weinberg equilibrium (HWE) in case or control groups. The ITGAV SNP genotypes and alleles frequencies for patients and controls are presented in Table 2. The overall distribution of genotypes and alleles in all SNPs in ITGAV in RA patients were similar to those in control group.

The distribution of ITGAV rs3911238-G/C genotype and C allele in patients with moderate-to-high RA activity and RA patients with anti-CCP antibody were significantly different from those in patients with remission-to-low disease activity ($\chi2$=4.6, $p$=0.048 and $\chi2$=4, $p$=0.041, respectively) and RA patients without anti-CCP antibody ($\chi2$=15, $p$=0.001 and $\chi2$=3.5, $p$=0.066), respectively (Table 3).

Among ITGAV SNPs, we found that only ITGAV-rs3911238-G/C polymorphism was associated with the severity of RA (remission-to-low and moderate-to-high). The odd ratio (OR) was 1.53 for codominant (CC vs. GG; 95% (CI) =1.02-2.3; $p$=0.041] and 1.18 for ITGAV allele [C vs. G; 95% CI=1.01-1.4; $p$=0.042]. In addition, ITGAV-rs3911238-G/C polymorphism was associated with the presence of anti-CCP antibody in RA patients in codominant model. Genotypes: [CC vs. GG: OR=2.77 (1.53-5.1), $p$=0.001] and allele [C vs. G: OR=1.19 (1.02-1.4), $p$=0.033)] (Table 4).

As shown in Table 5, among the SNPs of ITGAV polymorphisms, only presence of the ITGAV rs3911238-G/C polymorphism significantly affected the ESR, CRP, anti-CCP, and activity values within RA patients.

**Table 3. Distributions of genotypes and alleles of four SNPs in ITGAV gene between RA patients with remission or low activity and moderate or high activity and between RA patients with positive or negative anti-CCP**

| Genotypes and alleles | RA patients with moderate or high activity (n=119) | RA patients with remission or low activity (n=300) | RA patients with anti-CCP positive (n=221) | RA patients with anti-CCP negative(n=198) |
|---|---|---|---|---|
| ITGAV rs3911238 genotypes | | | | |
| G/G | 61 (51.3%) | 178 (59.3%) | 121 (55%) | 118 (59.3%) |
| G/C | 46 (38.7%) | 107 (35.7%) | 76 (34.2%) | 77 (39.1%) |
| C/C | 12 (10.1%) | 15 (5%) | 24 (10.9%) | 3 (1.5%) |
| | ($\chi$2=4.6, $p$=0.048) | | ($\chi$2=15, $p$=0.001) | |
| ITGAV rs3738919 genotypes | | | | |
| C/C | 54 (45.4%) | 104 (34.8%) | 86 (38.6%) | 73 (36.9%) |
| C/A | 49 (41.2%) | 149 (49.8%) | 103 (46.8%) | 95 (48%) |
| A/A | 16 (13.4%) | 46 (15.4%) | 32 (14.5%) | 30 (15.2%) |
| | ($\chi$2=4.1, $p$=0.13) | | ($\chi$2=0.2, $p$=0.93) | |
| ITGAV rs3768777 genotypes | | | | |
| G/G | 58 (48.7%) | 133 (44.5%) | 105 (47.7%) | 86 (43.4%) |
| G/T | 46 (38.7%) | 112 (40.8%) | 90 (40.9%) | 78 (39.4%) |
| A/T | 15 (12.6%) | 44 (14.7%) | 25 (11.4%) | 34 (17.2%) |
| | ($\chi$2=0.7, $p$=0.7) | | ($\chi$2=3, $p$=0.23) | |
| ITGAV rs10174098 genotypes | | | | |
| A/A | 58 (49.2%) | 131 (44.1%) | 106 (48.4%) | 85 (42.5%) |
| A/G | 46 (39%) | 122 (41.1%) | 88 (40.2%) | 80 (40.7%) |
| G/G | 14 (11.9%) | 44 (14.8%) | 25 (11.4%) | 33 (16.6%) |
| | ($\chi$2=1.1, $p$=0.58) | | ($\chi$2=3.1, $p$=0.22) | |
| ITGAV rs3911238alleles | | | | |
| G | 168 (70.6%) | 463 (77.2%) | 318 (72.3%) | 313 (78.6%) |
| C | 70 (29.4%) | 137 (22.8%) | 124 (27.7%) | 83(21.4%) |
| | ($\chi$2=4, $p$=0. 041) | | ($\chi$2=4.6, p=0.033) | |
| ITGAV rs3738919 alleles | | | | |
| C | 157 (66%) | 357 (59.7%) | 275 (62.2%) | 239 (60.7%) |
| A | 81 (34%) | 241 (40.3%) | 155 (37.8%) | 155(39.3%) |
| | ($\chi$2=2.84, $p$=0. 093) | | ($\chi$2=0.21, $p$=0.64) | |
| ITGAV rs3768777 alleles | | | | |
| G | 162 (68.1%) | 388 (64.9%) | 302 (68.3%) | 248 (62.9%) |
| T | 76 (31.9%) | 210 (35.1%) | 140 (31.7%) | 146(37.1%) |
| | ($\chi$2=0.77, $p$=0. 38) | | ($\chi$2=2.7, $p$=0.1) | |
| ITGAV rs10174098 alleles | | | | |
| A | 162 (68.6%) | 384 (64.6%) | 302 (68.6%) | 244 (62.6%) |
| G | 74 (31.4%) | 210 (35.4%) | 138 (31.4%) | 146(37.4%) |
| | ($\chi$2=4, $p$=0. 041) | | ($\chi$2=3.5, $p$=0.066) | |

The RA patients with C/C genotype of ITGAV rs3911238 showed significantly increased number of swollen joints ($p$=0.001), higher ESR ($p$=0.03), CRP ($p$=0.004), anti-CCP ($p$<0.001) and disease activity score ($p$=0.024) compared to those with G/G genotype. In addition, haplotypes analysis showed that ITGAV rs3733891C/rs3768777T/rs3911238C/rs10174098A haplotypes increased the risk of RA (OR=5.54; $p$=0.049). In addition, ITGAV rs3733891A/rs3768777T/rs3911238G/rs10174098A haplotypes was associated with the presence of anti-CCP in RA patient (OR=2.89; $p$=0.024).


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**Table 4. Odd ratio of genotypes and alleles of four SNPs in ITGAV gene between RA patients with remission or low activity and moderate or high activity and between RA patients with anti-CCP positive and anti-CCP negative subjects**

| Genotypes and allele | RA patients with remission or low activity compared to moderate or high activity | RA patients with positive anti-CCP compared to negative anti-CCP patients |
|---|---|---|
| rs3911238 genotypes | | |
| C/C vs. G/G | 1.53 (1.02–2.3) p=0.041 | 2.77 (1.5–5.1), *p*=0.001 |
| C/G vs. G/G | 1.25(0.8–2) p=0.32 | 0.95 (0.6–1.4) *p*=0.82 |
| rs3738919 genotypes | | |
| A/A vs. C/C | 0.82 (0.59–1.14) p=0.23 | 0.95(0.7–1.3, *p*=0.7) |
| A/C vs. CC | 0.63 (0.4–1.004) p=0.052 | 0.91(0.6–1.34, *p*=0.62) |
| rs3768777 genotypes | | |
| T/T vs. G/G | 0.88 (0.64–1.23) p=0.46 | 0.77(0.57–1.1), *p*=0.08 |
| T/G vs. G/G | 0.87 (0.54–1.4) p=0.53 | 0.93 (0.61–1.4), *p*=0.71 |
| rs10174098 genotypes | | |
| G/G vs. A/A | 0.85(0.6–1.2, p=0.33) | 0.76(0.57–1.03, *p*=0.073) |
| A/G vs. A/A | 0.85 (0.62–1.2, p=0.29) | 0.78 (0.59–1.03, *p*=0.08) |
| rs3911238 alleles | | |
| G | 1.18 (1.01–1.4, p=0.042) | 1.19 (1.02–1.4, *p*=0.033) |
| C | | |

**Table 5. Comparison of ESR, CRP, anti-CCP levels, number of tender and swollen joints and DAS28-CRP among ITGAV rs3911238, ITGAV rs3733891, rs3768777 and rs10174098 genotypes**

| Variables | Number of Tender Joints | Number of Swollen Joints | ESR (mm/h) | CRP (mg/L) | Anti-CCP (RU/L) | DAS28-CRP |
|---|---|---|---|---|---|---|
| rs3911238 | | | | | | |
| GG vs. C/G | 1.8±2.6 vs. 2.2±3.1 *p*=0.2 | 0.65±1.4 vs. 0.79±1.7 *p*=0.21 | 17.2±13.7 vs. 9.4±15.5 *p*=0.34 | 5.2±6.2 vs. 6.5±7.4 *p*=0.037 | 33.5±38.5 vs. 42.7±47.6 *p*=0.2 | 2.5±1.1 vs. 2.7±1.16 *p*=0.043 |
| G/G vs. C/C | 1.8±2.6 vs. 2.01±2.1 *p*=0.1 | 0.65±1.4 vs. 1.3±1.9 *p*=0.001 | 17.3±13.7 vs. 25.3±23.5 *p*=0.03 | 5.2±6.2 vs. 9.2±10.2 *p*=0.004 | 33.5±38.5 vs. 76.5±83 *p*<0.001 | 2.5±1.1 vs. 3±1.14 *p*=0.024 |
| CC vs. CG | 2.01±2.1 vs. 2.2±3.1 *p*=0.36 | 1.3±1.9 vs. 0.79±1.7 *p*=0.015 | 25.3±23.5 vs. 18.9±15.5 *p*=0.031 | 8.5±10.2 vs. 6.5±7.4 *p*=0.14 | 76.5±83 vs. 42.7±47.6 *p*=0.004 | 3±1.14 vs. 2.7±1.16 *p*=0.22 |

## DISCUSSION

Recently the polymorphism of the integrin αv subunit encoded by the ITGAV gene is considered as RA susceptibility loci. However, at the present, no information is available on the clinical significance of this observation and association of ITGAV rs3911238-C allele with systemic inflammatory markers (CRP, anti-CCP, ESR) and severity of RA activity (DAS28).

The present case-control study is the first investigation demonstrating a significant correlation between ITGAV rs3911238-G/C polymorphism and anti-CCP antibody, CRP, ESR, and the risk and severity of RA in Iranian population. We found that ITGAV rs3911238-C/C genotype and ITGAV rs3911238-C allele increased the severity of RA by 1.53 and 1.18 folds, respectively. In RA patients, ITGAV rs3911238-C/C genotype and ITGAV rs3911238-C allele increased the presence of anti-CCP antibody by 2.77 and 1.19 times, respectively.

The RA patients with C/C genotype of ITGAV-rs3911238 showed significantly higher anti-CCP, CRP, ESR, and score of RA activity compared to RA patients with G/G and C/G genotypes. These novel findings suggest that the contribution of C/C genotype and C allele of ITGAV rs3911238 in severity of RA is due to

increased inflammatory markers such as anti-CCP, CRP and ESR. These data provide evidence of a link between rs3911238-*C* allele of the ITGAV gene with systemic inflammation and the severity of RA and nominates ITGAV-rs3911238-*C* allele as a new minor RA susceptibility gene in the Iranian population.

This is the first time that the ITGAV rs3911238-G/C polymorphism has been shown to be associated with RA. Recently, Inamine and coworkers demonstrated that SNP -rs3911238 in ITGAV is associated with the jaundice type progression of primary biliary cirrhosis (PBC). However, no significant association between ITGAV- rs3738919 polymorphisms in Japanese patients with PBC and control group was observed.[4] As we know, angiogenesis plays an important role in many chronic liver diseases including primary biliary cirrhosis (PBC).[22] As a result of our study, SNP rs3911238 showed association with higher inflammation parameters. Thus, it is possible to hypothesis that its association with other inflammatory conditions like cirrhosis may be due to increased inflammation in addition to angiogenesis. Another interesting result in this study was the association of ITGAV rs3911238-G/C polymorphism with the presence of anti-CCP antibody in RA patients. As we know, the presence of anti-CCP antibody is associated with more progressive RA and worse prognosis.[23,26] Based on this fact, ITGAV rs3911238-G/C polymorphism may be involved indirectly in RA prognosis through increasing anti-CCP antibody production.

A growing number of studies have revealed that polymorphisms in Integrin αVβ6 target sites affect the pathogenesis of RA disease. [13,14,24] In this study, the overall distribution of four ITGAV SNP genotypes and alleles in RA patients were similar to those in control group. In addition, three SNPs in ITGAV (rs3738919, rs10174098, and rs3768777) genotypes were not associated with severity of RA and presence of anti-CCP antibody. Jacq et al.[13] and Hollis-Moffatt and coworkers[24] have demonstrated that rs3738919-C allele of the ITGAV gene was associated with RA in the European Caucasian population, suggesting ITGAV as a new minor RA susceptibility gene. However, no significant associations between ITGAV rs3768777 polymorphisms in European Caucasian patients with RA were observed. In addition, Likuni et al.[25] and Hollis-Moffatt et al.[24] did not observe a significant association between rs3738919-C and rs10174098-A alleles of the ITGAV gene and RA in the Japanese, New Zealand (NZ), or Oxford (UK) populations, respectively. Further studies in other ethnic groups are necessary to draw definite conclusions.

In conclusion, our findings suggest that ITGAV-rs3911238-C allele is a risk factor for of RA activity. The carriers of C allele of ITGAV- rs3911238 have distinctly elevated serum levels of CRP, anti-CCP, and ESR value, suggesting that these individuals are more susceptible to progression of RA than the carriers of G allele of ITGAV rs3911238. Though, ITGAV rs3733891C/rs3768777T/rs3911238C/rs10174098A haplotypes were associated with the increased risk of RA in patients from Iran. However, further studies are needed to shed light on contribution of C allele of ITGAV- rs3911238 and its mechanism of action in the development of RA in different ethnicities.

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