Bionatura
Latin American Journal of Biotechnology and Life Sciences

Bionatura Issue 4 Vol 8 No 1 2023

Article

Association between Interleukin-17 rs2275913 G/A Gene Polymorphism and Susceptibility and Severity of Rheumatoid Arthritis in a sample of Iraqi patients

Mousa Abdul Hussein Taha[1,], and Da'ad Ali Hussain[2]*
[1] University of Baghdad, Institute of Genetic Engineering and Biotechnology for Postgraduate, Iraq
[2] University of Baghdad, Institute of Genetic Engineering and Biotechnology for Postgraduate, Iraq
** Correspondence: mousaalzurkany@gmail.com*
Available from: http://dx.doi.org/10.21931/RB/CSS/2023.08.04.31

ABSTRACT
Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial hyperplasia, cartilage damage, and bone erosions. Rheumatoid arthritis occurs in about 5 per 1,000 people and can lead to severe joint damage and disability. The clinical manifestations of symmetrical joint involvement include arthralgia, swelling, redness, and even limiting the range of motion. This study investigated the role of IL-17A rs2275913 G\A gene polymorphisms associated with susceptibility and severity to clinic pathological features of rheumatoid arthritis in a sample of Iraqi patients. The study includes one hundred subjects of Iraqi patients in the Rheumatology Unit of AL-Hindyia General Hospital in Karbala province. Samples were divided into two groups. The first group included patients, while the second group included those who were healthy. DNA was extracted, then the Genotyping polymorphism (rs2275913) of the gene Interleukin-17 was done by RT-PCR. The genotyping and allele frequencies of IL-17 rs2275913 G/A for the two groups showed no significant differences in genotype between patients and controls. Compared to the GA genotype between control and patients, the heterozygous GA genotype was not significantly different from controls (X^2=0.614, OR=0.166), and the TT genotype had no significant differences for RA (X^2=0.436, OR=1)

Keywords: Rheumatoid arthritis (RA), genetic polymorphism, RF, CRP and IL-17 level

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by synovial hyperplasia, cartilage damage, and bone erosions. Rheumatoid arthritis occurs in about 5 per 1,000 people and can lead to severe joint damage and disability. The clinical manifestations of symmetrical joint involvement include arthralgia, swelling, redness, and even limiting the range of motion [1]. RA is a persistent inflammatory disorder that causes synovial inflammation and hyperplasia, autoantibody formation (rheumatoid factor [RF] and anti-citrullinated protein antibody (Anti-CCP), cartilage and bone loss, and other systemic symptoms [2]. The prevalence population varies according to both sexes (women are afflicted two to three times more frequently than males), age, and

race (frequency of new RA diagnoses peaks in the sixth decade of life) [3]. Rheumatoid Arthritis (RA) is an autoimmune disorder where multiple cytokines, including IL-17A and IL-17F, produced by T helper cell 17 (Th17), contribute to its pathogenesis. Th17 acts as a pathogenic driver by initiating inflammatory responses in joints, leading to bone and cartilage destruction in RA patients [4].

Cytokines have synergistic, antagonistic, redundant, and pleiotropic biological effects. They are classified as pro-inflammatory and anti-inflammatory. The balance of pro-inflammatory and anti-inflammatory cytokines appears to dictate the fate of T-cell polarization during the immune response [5]. The cytokines' significance in inflammation and potential as extracellular therapeutic targets in RA, a dysregulated systemic immune response leads to immune cell infiltration into the joint synovium [6]. Consequently, pro-inflammatory cytokines are overproduced [7]. These attract more inflammatory and immune cells, causing the production of further cytokines, chemokines, and matrix metalloproteinases, which destroy the joint. Therefore, inhibiting pro-inflammatory cytokines or their receptors presents a treatment option for RA patients [8]. There is no single test that can definitively diagnose RA. So, we can count the most important tests used for diagnosing RA based on clinical features, radiological findings and laboratory tests [9].

MATERIALS AND METHODS

One hundred volunteers were taken in this study. Fifty patients with RA and fifty healthy were randomly selected between November 2021 and February 2022 at the Rheumatology Unit of AL-Hindyia General Hospital in Karbala province. A questionnaire was taken from the patients, and the case sheet included age, gender, residence, height, weight, and previous history of the disease. In this study,100 volunteers were used and divided into two groups; the first group included patients, while the second group included healthy. Two ml of peripheral blood from all select subjects were collected and placed into a sterile plain tube that contained EDTA, and three ml of serum were collected and placed into a sterile plain tube. The blood and serum were placed in a cool - box under aseptic conditions and transferred to the laboratory. Serum CRP and RF were measured by the latex method. Serum IL-17 levels were measured by ELISA test. Genotyping of polymorphism rs2275913 of the IL-17 gene was done using Taq man SNP genotyping Assays. A set of primers was used to amplify specific regions within the IL-17 gene. The forward primer 5`-AACATGAATTTCTGCCCTTCCC-3` and the Reverse primer 5`-GGTCACTTACGTGGCGTGT-3`. Fam-Probe 5`-TCCTTCAGAAGAAGAGATTC-3`and Hex-Probe 5`-CCTTCAGAAGGAGAGATTC-3`. The thermal cycling program was as follows: Carryover prevention at 50 C° for 2 min, followed by enzyme activation at 95 C° for 10 min, followed by 40 cycles of two steps (the first one was denaturation at 95 C° for 30 seconds and the second step of annealing for 1 min sec (60 C°).

Statistical Analysis

The statistical analysis system- SAS (2018) program was used to detect the effect of different factors on study parameters. T-test and LSD test were used to significantly compare between means. The chi-square test was used to significant compare between percentage (0.05 and 0.01 probability). Estimate of Odd ratio in this study. SAS. 2018. Statistical Analysis System, User's Guide. Statistical. Version 9.6th ed. SAS. Inst. Inc. Cary. NC. USA

RESULTS

Distribution of Rheumatoid Arthritis Patients and Control Group According to Rheumatoid Factor.

Table (1) contains the percentage of patients with positive RF and those with negative RF. Most patients (64%) have positive RF, while the rest (36%) have negative RF with P-value < 0.008. The control group is divided into two subgroups. The first has a positive RF and consists of about 20% of the control group. The remaining 80 % of the control group has a negative RF.

RF	Cases (50)		Control (50)		OR	X^2	p-value
	Freq.	Perc.	Freq.	Perc.			
Positive	32	64.0	10	20.0			
Negative	18	36.0	40	80.0	1.81	7.0	0.008 **
Total	50	100.0	50	100.0	8	31	

Table 1. Rheumatoid factor of patients with rheumatoid arthritis and control group. OR: Odds Ratio, X2: Pearson's Chi-Square, P: Probability, HS: Highly- significant at P value < 0.01

Rheumatoid factors (RF) are found in various diseases, including autoimmune and non-autoimmune diseases and rheumatoid arthritis (RA). It has been proven that up to 4% of young people, healthy people and the elderly have [17]. According to our results, the sensitivity of the rheumatoid factor IgG test is 60 percent. The results of this study are consistent with those of a previous study that found sensitivity to rheumatoid factor IgG in the range of 60-80 percent [18]. RF was positive in 75% of RA patients compared to 5% among controls. The RF seropositivity varies among RA patients in different studies, ranging from 57% [to 19]. 90.3% [20]. and 100% ("The Clinical Significance of Interleukin-15 and Interleukin-17 in Patients with Rheumatoid Arthritis," 2014). In this study, 75% of RA patients were rheumatoid factor positive. This may be attributed to the size of study population and the method of estimation of RF positivity and titer used beside the time of patient's selection. Also, RF and anti-CCP are considered very helpful during the diagnosis of RA. However, anti-CCP shows a superior specificity than RF for diagnosing RA [21].

Distribution of Rheumatoid Arthritis Patients and Control Group According to C-reactive Protein.

The results of C-reactive protein (CRP) in the current study showed highly significant differences in patients with rheumatoid arthritis than healthy control (P = 0.001), as shown in table (2). The current study observed that CRP in patients with RA is positive in 44/50 (88%) and negative in 6/50 (12 %); furthermore, in the control group, CRP is positive in 7/50 (14 %) and negative in 43 /50 (86 %).

CRP	Cases (50)		Control (50)		OR	X^2	p-value
	Freq.	Perc.	Freq.	Perc.			
Positive	44	88.0	7	14.0	1.162	1.110	0.001**
Negative	6	12.0	43	86.0			
Total	50	100.0	50	100.0			

Table 2. Distribution of rheumatoid arthritis patients and control groups according to C-reactive protein.OR: Odds Ratio, X2: Pearson's Chi-Square, P: Probability, HS: highly significant, P value (P < 0.01)

C-reactive protein sensitivity was found to be around 88 % in the current study, indicating that it has high specificity in RA patients. This result agreed with CRP seropositivity was 82.5% and 7.5% for RA patients and controls, respectively. C reactive protein (CRP) provides suitable information about the acute phase response [22]. However, in the state, the lack of the disease activity score index (DAS28) may influence the association of CRP with RA patients. This is also contrary to a study in which the level of CRP was shown to be significantly correlated with the severity of RA [23]. In this study, RA patients 44/50 (88%) showed positive for CRP, while 7/50 (14 %) were negative for CRP (Table 4-5). It is indicated that CRP can be used as a serum marker for RA [24].

Following an inflammatory event, IL-6 stimulates hepatocytes to produce the acute-phase reactant C-reactive protein (CRP) [27]. Smooth muscle cells, macrophages, endothelial cells, lymphocytes, and adipocytes have also been shown to express CRP [28]. CRP binds to immunoglobulin Fc gamma receptors (FcgR), causing pro-inflammatory cytokines to be generated, resulting in an inflammatory amplification loop [29]. CRP can play a direct role in bone degradation in RA, according to may preclinical evidence. The activation of receptor activator of nuclear factor-kB ligand (RANKL) expression, which activates osteoclast genesis and leads to bone resorption, causes bone degradation. In the absence of RANKL, CRP induces RANKL expression in peripheral blood monocytes and promotes osteoclast differentiation [30]. According to the core components of the 28-joint Disease Activity Score, higher CRP levels are correlated with greater RA disease activity (DAS28) [31].

3.3. Measurement of Interleukin-17 Level of RA Cases and Control Groups:

The concentration levels of IL17 in RA cases increased significantly (P<0.016) in RA patients with mean ± std error (148.06±11.834) in comparison with control with mean ± std error (121.12±3.663) that shown in table (3)

Variables	Mean ± Std error	T-test	P-Value
IL_17 Cases	148.061 ± 11.834	3.174**	0.016
IL_17 Control	121.126 ± 3.663		
* (P≤0.05), ** (P≤0.01).			

Table 3. IL-17 distribution among RA patients and control groups.T-test at significant 0.05**

The present study showed a significant difference in IL17 between the RA patient group and the healthy control group, and these observations were consistent with other previous studies in Iraq and other countries. Serum IL17 concentrations were significantly higher in the Iraqi sample of RA patients compared to controls.

This may help in the diagnosis of RA and suggest potentially an effective treatment [32]. Another Iraqi study present that the significantly higher levels of IL-17 among RA patients than the control group. This observation is consistent with several studies [33]. In the Tunisian population, Plasma IL-17 concentration was significantly higher in RA patients than in controls [34].

The important role of IL17 in some autoimmune diseases, especially with RA disease [35]. These findings may be according to the fact that IL17 has a main role in stimulating other pro-inflammatory agents and aids in the accumulation of dendritic cells, monocytes, neutrophils and TNFα that lead to inducing of inflammation and then the progress of the disease to reach destruction of joint [36,37]. This result agrees with the finding of [38]. Who referred to elevation of IL17 and IL22 in RA patients compared to osteoarthritis patients and healthy controls. Some other studies reported an increase in IL 17 levels and its role in the pathogenesis of RA [39,40]

3Genotype Distribution and Allele Frequency of IL-17 rs2275913 G/A in Patients and Control Groups

The genotype and allele frequencies of the IL-17 rs2275913 G/A for the two study groups (controls and patients) are shown in Table (4). All genotype frequencies of the control and patient groups confirmed the Hardy-Weinberg equilibrium (HWE).

Genotype rs2275913 G/A	**Patients No. (%)**	**Control No. (%)**	**Chi-Square (χ^2)**	**P-value**	**OR (CI.)**
GG	36 (72.00%)	34 (68.00%)	0.436 NS	0.815	Ref. =1
GA	6 (12.00%)	4 (8.00%)	0.614 NS	0.393	0.166 (0.06-0.49)
AA	8 (16.00%)	12 (24.00%)	0.436 NS	0.801	0.209 (0.11-0.46)
Total	50 (100%)	50 (100%)			
Allele	**Frequency**				
G	0.78	0.72	---		
A	0.22	0.28			
NS: Non-significant.					

Table 4. Genotype distribution and allele frequency of rs2275913 G/A in patients and control groups.OR: odds ratio; X²: Person's Chi Square

The detection of the genotype of IL-17 G\A rs2275913 gene polymorphism with allele frequencies between the study groups (patients and control), as shown in Table (4), revealed a significant increase of GG genotype in RA patients with a percentage of 72% compared with control groups with 68%, respectively with P≤ 0.815. Moreover, there was a significant decrease of AA genotype in RA Patients with a percentage of 16% compared with control groups with a percentage of

24%, with P≤0.801. In addition, there was a significant increase in GA IL-17 genotype in a patient group with a percentage of 12% compared with control groups with a percentage (8%) with P≤0.393.

This study could be explained as a protective homozygous genotype AA of IL-17 rs2275913 G/A. In other words, the A allele is a protective allele for skeletal tissue by holding back the activity of osteoclasts genetically contrary to the G allele [44]. This study found no significant association between IL-17A rs2275913 and disease susceptibility. This result confirmed a previous report on the Tunisian population [45]. Again, most of the published studies were performed in Algerian [46] and Polish [47]. Brazilian [48]. and Chinese populations emphasized the lack of association between the IL-17A rs2275913 and RA risk.

Nevertheless, two studies performed in Norway and Brazil reported that the rs2275913 polymorphism increased the risk of RA. In Norwegian patients, the IL-17AG allele conferred a weak risk [49]. At the same time, the risk for RA was moderate for the IL-17G/G genotype in the Brazilian study [50]—accordingly, the meta-analysis of [51]. The IL-17 AA allele conferred a weak protective role for RA risk. In this meta-analysis, the highest weight of the included studies was for the Norwegian report [52], as it involved 950 RA patients and 933 healthy controls. Therefore, the risk conferred by IL-17A rs2275913 G allele in RA predisposition might be weak. This could explain the absence of association reported in the mainstream of published studies and the present study. Besides, we did not note any association between IL-17A polymorphism and RA activity. This data corroborates the results of previous reports in diverse populations. However, [53] reported that patients with one copy of the IL-17AA allele were good responders to methotrexate therapy. Likewise, the IL-17G/G genotype was predictive for the highest activity in patients under anti-TNF therapy in a Polish study [54]. The rs2275913 polymorphism in the IL-17A gene is located in the promoter at position -197. Until now, its functional impact is unknown, but the current data suggest it may enhance the promotor activity, resulting in a higher cytokine secretion. So far, IL17 gene polymorphisms have not been widely investigated in RA patients. When examining the association between IL17A gene polymorphisms and RA in Norway and New Zealand patients [55]. A weak association between RA and the promoter SNP rs2275913 was found in the Norwegian population. This association was not replicated in the RA cohort from New Zealand.

Our study has potential limitations, which could contribute to the false positive or negative results. First, our sample size may not be large enough to detect an association of a gene with the same effect of RA. Our control groups were smaller than RA groups, so the power of this study is not too high. Nevertheless, the analysis of polymorphisms should rely on clinically well-described groups and not just on the sample size. Unfortunately, in our study, only one SNPs was tested in patients with RA and control. These findings demonstrated that the IL-17 F variant might be associated with increased disease activity in Iraqi patients with RA. However, further studies associated with IL-17F expression and its genetic analysis in large RA cohorts with clinical data are warranted [60]. So, the results of this study suggest that IL17A gene polymorphism is not an important factor associated with susceptibility and some clinical parameters of RA in the Iraqi population. Nevertheless, this hypothesis requires further investigation.

The data of allele frequencies of point mutation on IL-17 rs2275913 G/A gene polymorphism in two study groups (control and patients) are presented in Table (4). For the patients' group, the allele frequency of (G) was 0.78 %, but (A) allele frequency was 0.22 % according to the Hardy-Wienberg equation. In comparison, for control groups, the allele frequency of (G) was 0.72 %, but the

(A) allele was 0.29 % according to the Hardy-Wienberg Equation (HWE) (Table 4). Table (4) shows no significant differences in allele frequencies of IL-17 rs2275913 G/A gene polymorphism with the risk of rheumatoid arthritis in a sample of Iraqi Patients.

DISCUSSION

This higher proportion of RF-positive patients compared to RF-negative patients is attributed to the fact that these antibodies are pentameric IgM antibodies that bind to the Fc portion of human immunoglobulin G, making it elevated in autoimmune disease or inflammation, as well as in healthy patients, rheumatoid arthritis is an inflammatory disease, so this will cause this protein to be elevated [10].

Rheumatoid Factor (RF) has been widely used as a screening test for patients with arthritis. A recent study revealed that RF titer reflected RA disease activity [11]. However, RF is present in patients with other autoimmune and infectious diseases and even in a noticeable proportion of normal healthy subjects, particularly those aged [12]. Rheumatoid factor values in patients seem inconsistent, where [13]. demonstrated that (77.1 %) of RA patients were positive and (22.9 %) were negative [14]. However, several Iraqi studies demonstrated that all patients had a positive result for RF [15]. High serum levels of RF are a hallmark of rheumatoid arthritis and can be used to monitor disease activity [16].

Furthermore, IL-17 is a potent inducer of CRP from human smooth muscle cells and hepatocytes [25]. Another recent study showed that the percentage of Th17 cells in SF positively correlated with CRP) and There were direct significant correlations between serum IL-17 levels and inflammatory markers as ESR and CRP and serological markers as anti-CCP [26].

Interleukin-17 is one of the important cytokines that have a vital role in developing and progressing RA disease's pathogenicity and is used as a target site for biological treatment. [41]. That interleukin 17 aids in the secretion of another pro-inflammatory cytokine (IL6, IL1, IL8 and tumor necrosis factor-α), which can be manifested in synovial fluid and serum of RA patients [42,43].

In this study, the IL-17A AA genotype showed a significant association with RA. However, these results contradict a previous study in which the IL-17A GG genotype increased RA susceptibility among Caucasian populations. Thus, population deference could be the main reason since the IL-17A GG genotype was not associated with RA susceptibility among Mongolians. IL-17A genotypes were not associated with RA susceptibility in Egyptian and Polish populations. Furthermore, in a study conducted among a Tunisian population, IL-17A polymorphisms did not show any significant association with RA prevalence [56]. Significant relationships were discovered between inflammatory illnesses, the IL-17A rs2275913 A versus G allele, and the GA vs. GG genotype in the codominant model. According to this data, those with the rs2275913 A allele or GA genotype had a 20% or 41% higher risk of inflammatory disorders than those with the G allele or GG genotype, respectively [57]. They observed significant relationships between the rs2275913 G allele and osteoarthritis in 19 studies involving 5298 cases and 5675 healthy controls. IL-17A gene rs2275913 G allele protects against osteoarthritis susceptibility in Mongolians [58]. Another study on osteoarthritis in the Han Chinese population found that IL-17 gene polymorphisms may be linked to the prevalence of high-risk knee osteoarthritis [59].

CONCLUSION

The current study observed that the RF in patients with RA was positive in (64%) and negative in (36%); additionally, in a control group, RF was negative in (80%) and 20%). The current study observed that CRP in patients with RA is positive in (88%) and negative in (12 %); furthermore, in the control group, CRP is positive in (14 %) and negative in (86 %). The concentration levels of IL17 in RA cases increased significantly ($P<0.016$) in RA patients with mean ± std error (148.06±11.834) in comparison with control with mean ± std error (121.12±3.663). The genotyping and allele frequencies of IL-17 rs2275913 G/A for the two groups showed no significant differences in genotype between patients and controls. Compared to the GA genotype between control and patients, the heterozygous GA genotype was significantly different from controls ($X^2=0.614$, OR=0.166), and the GG genotype significantly increased risk for RA ($X^2=0.436$, OR=1). In addition, allele frequency for the G allele is associated with a significantly increased risk for RA. For the patient's group, the allele frequency of (G) was 0.78 %, but (A) allele frequency was 0.22 %, while for control groups, the allele frequency of (C) was 0.72 %, but (A) allele was 0.28 %. Moreover, the IL-17 rs2275913 G/A genotype was not associated with increased risk for the development of RA in Iraqi patients.

References

1. Guo, Q., Wang, Y., Xu, D., Nossent, J., Pavlos, N. J., and Xu, J. (2018). Rheumatoid arthritis: pathological mechanisms and modern pharmacologic therapies. Bone research,
2. Rivellese F, Lobasso A, Barbieri L, Liccardo B, de Paulis A, Rossi FW. (2019). Novel therapeutic approaches in rheumatoid arthritis: role of Janus kinases inhibitors. Curr Med Chem.;26(16):2823–43.
3. Littlejohn EA, Monrad SU. (2018). Early Diagnosis and Treatment of Rheumatoid Arthritis. Prim Care.;45(2):237–55.
4. Amin, Amna Sheikh, Nadeem Mukhtar, Maryam Saleem, Tayyaba Akhtar, Tasleem Fatima, Naz Mehmood, Rabia. (2021). Association of interleukin-17 gene polymorphisms with the onset of Rheumatoid Arthritis
5. Romero-Adrian, T.B.; Leal-Montiel, J.; Monsalve-Castillo, F.; Mengual- Moreno, E.; García McGrego, E.G.; Lenis Perini, L. and Antúnez, A. (2009). Helicobacter pylori: Bacterial Factors and the Role of Cytokines in the Immune Response. Current Microbiology, 60(2): 143-155.
6. MELLADO M, MARTÍNEZ-MUÑOZ L, CASCIO G, LUCAS P, PABLOS JL, RODRI-GUEZ-FRADE JM. (2015). T cell migration in rheumatoid arthritis. Front Immunol; 6: 384.
7. MCINNES IB, LIEW FY: (2005). Cytokine networks—towards new therapies for rheumatoid arthritis. Nat Clin Pract Rheumatol; 1: 31–
8. MCINNES IB, SCHETT G. (2011). The pathogenesis of rheumatoid arthritis. N Engl J Med; 365: 2205–19.
9. Ebel and O'Dell., 2021. Ebel, A. V., and O'Dell, J. R. (2021). Clinical features, diagnosis, and treatment of rheumatoid arthritis. Physician Assistant Clinics, 6(1):41-60.
10. Fleischmann R. (2018). To facitinib in the treatment of active rheumatoid arthritis in adults. Immunotherapy.;10(1):39–56.
11. Manhal, F. S. (2009). Cytokine Profile in Patients with Rheumatoid Arthritis. Fac Med Baghdad, Vol. 51, No. 4.
12. Westwood, O. M., Nelson, P. N., Hay, F. C. (2006). Rheumatoid factors: what's new. Rheumatology, 45(4):379–385.
13. Artur Z., and Brikena S. (2015). The Relationship of Rheumatoid Factor with Disease Activity in Patients with Rheumatoid Arthritis. IJSR Vo 4.
14. Artur Z., and Brikena S. (2015). The Relationship of Rheumatoid Factor with Disease Activity in Patients with Rheumatoid Arthritis. IJSR Vo 4.

15. Ahmed, Mohanad M Al-Ruhaimi, Khalid A Obaid Mohammed, Suhad Hadi (2010). Evaluation of the rheumatoid factors of the IgG, IgM and IgA isotypes as prognostic parameters for rheumatoid arthritis among Iraqi patients
16. Meyer, O., Combe, B., Elias, A., Benali, K., Clot, J., Sany, J., et al. (1997). Autoantibodies predicting the outcome of RA: Evaluation in two subsets of patients according to the severity of radiographic damage. Ann Rheum Dis, 56 (11): 682-685
17. Listing J, Kekow J, Manger B, Burmester G-R, Pattloch D, Zink A, et al. (2015). Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab. Ann Rheum Dis.;74(2):415–21.
18. Dessie G, Tadesse Y, Demelash B, Genet S. (2020). Assessment of Serum Lipid Profiles and High-sensitivity C-reactive Protein Among Patients Suffering from Rheumatoid Arthritis at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia: A Cross-Sectional Study. Open Access Rheumatol Res Rev.; 12:223.
19. Barakat AM, Hasony HJ, Al-Khafaji aT. (2009). Diagnostic value of antibodies to citrullin-containing peptides in patients with rheumatoid arthritis in southern Iraq. Basrah Journal of Surgery; 15:43-50.
20. Kobak S. (2011). Demographic, clinical, and serological features of Turkish patients with rheumatoid arthritis: evaluation of 165 patients. Clin Rheumatol.; 30:843–47.
21. Heidari B, Lotfi Z, Ali Firouzjahi R, et al. (2010). Comparing the diagnostic values of Anti-cyclic citrullinated peptide antibodies and rheumatoid factor for rheumatoid arthritis. Res Med; 33: 156–161.
22. Heidari B, Hajian K and Jahi AF. (2004). Correlation between serum CRP levels and disease activity in rheumatoid arthritis. Kowsar Med J; 9: 208220.
23. Grassi W, De Angelis R, Lamanna G, et al. (1998). The clinical features of rheumatoid arthritis. Europ J Radiol; 27: S18–S24.
24. Kadir, Y., Saliha, K., Rabia, C., Mahir, U., and Kazim, F. (2003). Fibrinogen versus conventional acute phase reactants in the assessment of disease activity in Rheumatoid arthritis. Fiziksel Tip, 6(2): 11-15.
25. Koenders MI, Lubberts E, Loo FA, OppersWalgreen B, Bersselaar L , Helsen MM, et al. (2006). Interleukin-17 Acts Independently of TNFa under Arthritic Conditions. J Immunol.; 176:6262-69.
26. Gullick NJ, Evans HG, Church LD, Jayaraj DM, Filer A, Kirkham BW et al. (2010). Linking power Doppler ultrasound to the presence of Th17 cells in the rheumatoid arthritis joint. PLoS One.;5: e12516.
27. Choy E, Rose-John S. (2017). Interleukin-6 as a multifunctional regulator: inflammation, immune response, and fibrosis. J Scleroderma Relat Disord.;2(2_suppl): S1–5.
28. Sproston, N. R., and Ashworth, J. J. (2018). Role of C-reactive protein at sites of inflammation and infection. Frontiers in immunology, 9, 754.
29. Newling M, Sritharan L, van der Ham AJ, Hoepel W, Fiechter RH, de Boer L, et al. (2019). C-reactive protein promotes inflammation through FcγRinduced glycolytic reprogramming of human macrophages. J Immunol.;203(1):225–35.
30. Kim K-W, Kim B-M, Moon H-W, Lee S-H, Kim H-R. (2015). Role of C-reactive protein in osteoclastogenesis in rheumatoid arthritis. Arthritis Res Ther.;17(1):1–12.
31. Cylwik B, Chrostek L, Gindzienska-Sieskiewicz E, Sierakowski S, Szmitkowski M. (2010). Relationship between serum acute-phase proteins and high disease activity in patients with rheumatoid arthritis. Adv Med Sci.;55(1):80–5.
32. Abdullah, Rabab Mahmood Khalil, A A Jassim, Nizar Abdulateef Gorial, Faiq Isho. (2013). Serum IL17 and IL6 levels in a Sample of Iraqi Patients with Rheumatoid Arthritis: A Case-Control Study
33. Metawi SA, Abbas D, Kamal MM, Ibrahim MK. (2011). Serum and synovial fluid levels of interleukin-17 in correlation with disease activity in patients with RA. Clin Rheumatol.;30:1201–7.
34. Dhaouadi, T.; Chahbi, M.; Haouami, Y.; Sfar, I.; Abdelmoula, L.; Abdallah, T., and Gorgi, Y. (2018). IL-17A, IL-17RC polymorphisms and IL17 plasma levels in Tunisian patients with rheumatoid arthritis. In PLoS ONE 13(3):
35. Korn T, Bettelli E, Oukka M. (2009). IL-17 and Th17 cells. Annul Rev Immunol.;27:485–517.
36. Chabaud, M., Durand, J. M., Buchs, N., Fossiez, F., Page, G., Frappart, L. and Miossec, P. (1999). Human interleukin-17: a T cell-derived pro-inflammatory cytokine produced by the rheumatoid synovium. Arthritis Rheum. 42:963-970.

37. Shahrara, S., Pickens, S.R., Mandelin II, AM., Karpus, W.J., Huang, Q., Kolls, J.K., et al. (2010). IL-17-mediated monocyte migration occurs partially through CC chemokine ligand 2/monocyte chemoattractant protein-1 induction. J Immunol; 184:4479-87.
38. Zhang, L., Li, JM., Liu, XG., Ma, DX., Hu NW, Li YG, et al. (2011). Elevated Th22 cells correlated with Th17 cells in patients with rheumatoid arthritis. J Clin Immunol; 31:606-14.
39. Kokkonen, H., Söderström, I., Rocklöv, J., Hallmans, G., Lejon, K., Rantapää Dahlqvist, S. (2010). Up-regulation of cytokines and chemokines predates the onset of rheumatoid arthritis. Arthritis Rheum; 62:383-91
40. Chen, DY., Chen, YM., Chen, HH., Hsieh, CW., Lin, CC., Lan, JL. (2011). Increasing levels of circulating Th17 cells and interleukin-17 in rheumatoid arthritis patients with an inadequate response to anti-TNF-α therapy. Arthritis Res Ther;13: R126.
41. Kirkham, B.W., Lassere, M.N., Edmonds, J.P., Juhasz, K.M., Bird, P.A., Lee, C.S., et al. (2006). Synovial membrane cytokine expression is predictive of joint damage progression in rheumatoid arthritis: a two-year prospective study (the DAMAGE study cohort). Arthritis Rheum; 54:1122-31
42. Jovanovic DV, Di Battista JA, Martel-Pelletier J, Jolicoeur FC, He Y, Zhang M, Mineau F, Pelletier JP. (1998). IL-17 stimulates the production and expression of pro-inflammatory cytokines, IL-beta and TNF-alpha, by human macrophages. J Immunol.;160:3513–21.
43. JPGM;(50):60–68.
44. Kotake, S., Udagawa, N., Takahashi, N., et al. (1999). IL-17 in synovial fluids from patients with rheumatoid arthritis is a potent stimulator of osteoclastogenesis. J Clin Invest; 103:1345-52.
45. Salman, Asmaa Mahmoud, Hussain, Da′ad A. (2021). Investigation the Role of IL-17 rs2275913 Gene Polymorphism with the Risk of Osteoporosis in a Sample of Iraqi Pre and Postmenopausal Women
46. Dhaouadi, T.; Chahbi, M.; Haouami, Y.; Sfar, I.; Abdelmoula, L.; Abdallah, T., and Gorgi, Y. (2018). IL-17A, IL-17RC polymorphisms and IL17 plasma levels in Tunisian patients with rheumatoid arthritis. In PLoS ONE 13(3):
47. Louahchi S, Allam I, Boucharef A, Abdesemed A, Khaldoun N, Nebbab A, et al. (2016). Association of single nucleotide polymorphisms of IL23R and IL17 in rheumatoid arthritis in the Algerian population. Acta Reumatol Port; 41: 151–157. PMID: 27606475
48. Pawlik A, Kotrych D, Malinowski D, Dziedziejko V, Czerewaty M, Safranow K. (2016). IL17A and IL17F gene polymorphisms in patients with rheumatoid arthritis. BMC Musculoskelet Disord; 17: 208. https:// doi.org/10.1186/s12891-016-1064-1 PMID: 27169372
49. Nunes Carvalho C, Feliciano do Carmo R, Pinto Duarte AL, Albuquerque Tavares Carvalho A, Leao JC, Gueiros LA. (2015). IL-17A and IL-17F polymorphisms in rheumatoid arthritis and Sjo¨gren's syndrome. Clin Oral Invest; 20: 495–502.
50. Nordang GBN, Viken MK, Hollis Moffatt JE, Merriman TR, Forre O, Helgetveit K, et al. (2009). mAssociation analysis of the interleukin 17A gene in Caucasian rheumatoid arthritis patients from Norway and New Zealand. Rheumatology; 48:367–370.
51. Dhaouadi, T.; Chahbi, M.; Haouami, Y.; Sfar, I.; Abdelmoula, L.; Abdallah, T., and Gorgi, Y. (2018). IL-17A, IL-17RC polymorphisms and IL17 plasma levels in Tunisian patients with rheumatoid arthritis. In PLoS ONE 13(3):
52. Lee, Y., and Bae, S. (2017). Associations between circulating IL-17 levels and rheumatoid arthritis and between IL-17 gene polymorphisms and disease susceptibility: A meta-analysis. Postgraduate Medical Journal, 93(1102):
53. Nordang GBN, Viken MK, Hollis Moffatt JE, Merriman TR, Forre O, Helgetveit K, et al. (2009). mAssociation analysis of the interleukin 17A gene in Caucasian rheumatoid arthritis patients from Norway and New Zealand. Rheumatology; 48:367–370.
54. Dhaouadi, T.; Chahbi, M.; Haouami, Y.; Sfar, I.; Abdelmoula, L.; Abdallah, T., and Gorgi, Y. (2018). IL-17A, IL-17RC polymorphisms and IL17 plasma levels in Tunisian patients with rheumatoid arthritis. In PLoS ONE 13(3):
55. Bogunia-Kubik K, Swierkot J, Malak A, Wysoczanska B, Nowak B, Bialowas K, et al. (2015). IL-17A, IL-17F and IL-23R polymorphisms in Polish patients with rheumatoid arthritis. Arch Immunol Ther Exp; 63:215–221.

56. Nordang GBN, Viken MK, Hollis Moffatt JE, Merriman TR, Forre O, Helgetveit K, et al. (2009). mAssociation analysis of the interleukin 17A gene in Caucasian rheumatoid arthritis patients from Norway and New Zealand. Rheumatology; 48:367–370.
57. Osman, Rgda Mohamed Noma, Mounkaila Ahmed, Abdallah Elssir, et al. (2021). Association of interleukin-17A rs2275913 polymorphism with rheumatoid arthritis susceptibility in Sudanese populationPotential Involvement of IL-17F in Asthma
58. Eskandari-Nasab, E.; Moghadampour, M., and Tahmasebi, A. (2017). Meta-analysis of risk association between interleukin-17A and F gene polymorphisms and inflammatory diseases. Journal of Interferon & Cytokine Research, 37(4),165–174.
59. Shao M, Xu S, Yang H, et al (2020). Association between IL-17A and IL-17F gene polymorphism and susceptibility in inflammatory arthritis: a meta-analysis. Clin Immunol 2020; 213: 108374.
60. Bai, Y.; Gao, S.; Liu, Y.; Jin, S.; Zhang, H., and Su, K. (2019). Correlation between Interleukin-17 gene polymorphism and osteoarthritis susceptibility in Han Chinese population. J. BMC Medical Genetics, 20(1): 1–7.
61. Paradowska-Gorycka A, Wojtecka-Lukasik E, Trefler J, Wojciechowska B, Lacki JK, Maslinski S. (2010). Association between IL-17F gene polymorphisms and susceptibility to and severity of rheumatoid arthritis (RA). Scand J Immunol.;72:134–41.

Received: May 15, 2023/ Accepted: June 10, 2023 / Published: June 15, 2023
Citation: Taha, M.A.H.; Hussain, DA. Association between Interleukin-17 rs2275913 G/A Gene Polymorphism and Susceptibility and Severity of Rheumatoid Arthritis in a sample of Iraqi patients. Revista Bionatura 2023;8 (2) 63. http://dx.doi.org/10.21931/RB/CSS/2023.08.04.31