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RESEARCH ARTICLE

Correlation Between Interleukin-17 Level and Genetic Polymorphism with Rheumatoid Arthritis.

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Abstract: This investigation is an attempt to examine the levels of IL-17A and the genetic polymor- phisms. This study comprised 100 patients (72 females, 28 males; age range 30–70 years) and 80 healthy controls (56 females, 24 males; age range 30–70 years) enrolled in the Rheumatology Unit. The age distribution of patients revealed that the age group of 41–50 years has the maximum prevalence of the disease, at 39%. The illness distribution is lowest among those aged 61–70, who comprise about 14% of all patients. The study revealed a significant gender disparity, with females accounting for 72% of the total number of patients and males accounting for 28%. The level of IL-17 was 103.43 ± 29.17 pg/mL compared with the healthy control group 60.12 ± 10.34 pg/mL at $P < 0.01$. The genotype frequency showed (GG, 41.25%; AA, 13.75%; GA, 45.00%) differs from that of the control group (GG, 50%; AA, 10%; GA, 40%) ($\chi 2 = 8.466$, df = 2, $P = 0.014$). The risk of RA was significantly increased by 3.73 times, with an OR of 3.73 (95% CI: 1.27–4.55, $P = 0.008$), due to the frequency of AA homozygotes being more significant in the RA group than in the control group (13.75% vs. 10%). Conversely, the heterozygous GA genotype was not substantially associated with the disease ($P = 0.113$). Compared to the mutant A allele, RA risk was 1.78 (OR = 1.78, 95% CI: 1.17 – 2.04; $P = 0.039$).
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Keywords: celiac disease, il 6, polymorphism.

INTRODUCTION

Rheumatoid arthritis (RA) is known by inflammation in joints, cartilage, and bone synovial tissue, and occasionally in areas outside joints [1]. A long-lasting, progressive, autoimmune inflammatory disorder, RA affects around one percent of the population in industrialized countries and is a major health and financial problem. Women become sick twice as often as men [2].

It is evident that genetic elements significantly influence the risk, severity, and progression of RA. Monozygotic twins exhibit RA in approximately 12–15% of instances, while the general population has a rate of about 1%, and fraternal twins or other first-degree relatives show rates of around 2–5% [3]. The low agreement suggests that environmental factors and the microbiome are additional factors contributing to the development of the disease. Additionally, gene sequences are not the only factors influencing heritability, as epigenetic modifications probably play a role, particularly in monozygotic twins [4].

IL-17A is the initial member of the cytokine family, which comprises six members. Its receptor (IL-17R) is present in a variety of cell types, including epithelial cells, B and T lymphocytes, fibroblasts, monocytes, and bone marrow stroma [5]. B cells, macrophages, neutrophils, and fibroblast-like synoviocytes are recruited and activated by IL-17 in both the early and late phases of rheumatoid arthritis, which is essential for osteoclastogenesis [5].

An important immunological mechanism and potential treatment target for different types of inflammatory arthritis may be the generation of IL-17 [6]. Th17 lymphocytes are the principal producers of IL-17A, but Tc lymphocytes, NK cells, eosinophils, and neutrophils may also con- tribute to its production [7]. Many cell types, including keratinocytes, fibroblasts, hematopoietic cells, epithelial and endothelial cells, and leukocytes, have the type 1 membrane-spanning protein known as the IL-17A receptor. It may bind to IL-17A, IL-17B, IL-17E, and IL-17F [8].

The current investigation aimed to examine the impact of gene polymorphisms and IL-17A levels on the severity and susceptibility of RA in Iraq.

MATERIAL AND METHODS

2.1 Patients

The study involved 100 patients and 80 healthy controls from the Baghdad Teaching Hospital Rheumatology Unit, aged 30–70 years, suffering from rheumatoid arthritis. Diagnosis was made by the consultant rheumatologist based on clinical and radiological examinations from January 20, 2023, to October 20, 2023, in Baghdad, Iraq.

2.2 Sample Collection

Eight milliliters of blood were collected from each participant. Five milliliters were placed into gel tubes for serum separation, and 3 mL into EDTA tubes. The serum was separated by cen- trifugation at 4000 rpm and stored at −20◦C for immunological testing.

2.2.1 Interleukin-17 Concentration

Laboratory Evaluations (Serum IL-17 Levels). The manufacturer's instructions (INNOVA BIOTECH CO) were followed to execute an enzyme-linked immunosorbent assay (ELISA).

2.3 DNA Extraction

Blood specimens were collected in EDTA-K-containing tubes and allowed to coagulate sponta- neously at room temperature after 30 minutes of incubation. Sediments were obtained by cen- trifuging the collection tubes at 2,500 r/min for 15 minutes. The samples were then stored in a cryopreservation container.

DNA was extracted over a six-month period using a nucleic acid purification kit according to the manufacturer's instructions. Following extraction, DNA samples were assessed for concentra- tion and purity, and subsequently stored in a freezer at −20 ◦C.

2.4 Genotyping

The authors, in collaboration with Bioneer Company (Korea), designed primers to amplify the IL-17A gene using a Thermal Cycler 9700 (Applied Biosystems, Foster City, CA, USA). The poly- merase chain reaction (PCR) produced a 426-bp fragment using the following primer sequences: forward 5'-ACATGAATTTCTGCCCTCC-3', and reverse 5'-AAATGCTGCACAATGACTTA-3'.

The PCR reaction was carried out in a total volume of 25 µL, containing 2 µL of DNA template, 0.5 µL of each primer (10 µmol/L), 9.5 µL of deionized water, and 12.5 µL of 2× Taq PCR Green Mix.

Thermal cycling conditions were as follows: initial denaturation at 94°C for 5 minutes; followed by 35 cycles of denaturation at 94°C for 30 seconds, annealing at 58°C for 30 seconds, and extension at 72°C for 30 seconds; with a final extension step at 72°C for 10 minutes.

PCR products were analyzed by agarose gel electrophoresis or stored at 4°C for subsequent processing. Genetic sequencing was performed by a sequencing company in Korea. Polymorphic locus genotypes were identified through direct sequencing and analyzed using SnapGene software. The distribution of genotype frequencies was evaluated based on the Hardy–Weinberg principle of genetic equilibrium.

2.5 Statistical Examination

For study analysis, SPSS (version 20.0) was employed for data analysis; continuous data was stated as mean ± standard deviation and categorical data as percentages. The ω2 test revealed a P-value of less than 0.05, indicating statistical significance, when genotype and allele variants were compared between the two groups.

RESULTS AND OBSERVATIONS:

3.1 Age distribution

The study reveals that patients aged 41-50 years have the highest prevalence of rheumatoid arthritis at 39%, according to the age distribution of patients. The age group aged 61-70 has the lowest disease distribution rate, accounting for 14% of the total number of patients, as displayed in Table 1.

Table 1: The patient age distribution in rheumatoid arthritis.

Age groups (Years)	Patients number (No.)	Percentage (%)
31-40	21	21%
41-50	39	39%
51-60	26	26%
61-70	14	14%
Total	100	100%

Past studies have shown that the prevalence of arthritis rises as people become older (OR = 1.100, 95% CI: 1.070 to 1.130, p < 0.0001) [9,10] noted that knee osteoarthritis and lower back pain risk increases considerably with age. The proportion of Americans with arthritis diagnosed by a doctor has risen from 7.1% in the 18-44 age bracket to 49.6% in the 65+ age bracket, according to research by [11]. More women than males suffer with RA [12].

3.2 Gender Distribution

Our current study's gender distribution results showed that rheumatoid arthritis was more com- mon in women (72% of all patients). In comparison, the condition was prevalent in men (28% of the total number of patients), as indicated in Table 2.

Table 2: The gender distribution of individuals with rheumatoid arthritis

Sex distribution	Number	%
Male	28	28%
Female	72	72%
Total	100	100%

[13] HAVE reported that RA is more prevalent in women than in men, with a female-to-male ratio ranging from 4:1 in younger individuals to less than 2:1 in senior populations [14]. While components linked with high estrogen levels may give protection, findings from several research point to a fast drop in oestrogenic function (seen during menopause or owing to anti-oestrogenic medications) as a risk factor for developing RA. Seronegative RA was more common in women who went through menopause early (before 44 years of age) in the Nurses' Health Study cohort compared to those who went through menopause later in life [15]. A study revealed that the use of anti-estrogenic medications like aromatase inhibitors or selective estrogen-receptor modulators increases the risk of RA in a dose-dependent manner [16]. Although oral contraceptives do include estrogens, it is unclear whether or not they increase the risk of RA [17]. Due to the higher estrogen levels originally delivered by oral contraceptives, older research suggests a potential dosage dependence since it suggests a more substantial protective impact on RA compared to later studies. In a large Swedish cohort, women who used oral contraceptives had a decreased risk of ACPA-positive rheumatoid arthritis in comparison to those who did not use them [18]. Swedish case-control research indicated that hormone replacement treatment decreased the likelihood of ACPA-positive rheumatoid arthritis in patients, except when patients were administered only oestrogen [19].

3.3 Level of IL-17

The present study estimated that the highest mean level of IL-17 in rheumatoid arthritis patients was (103.43 ± 29.17 pg/mL) compared with the healthy control group (60.12 ± 10.34 pg/mL) at ($P < 0.01$) as shown in Table 3.

Table 3: The level of IL-17 in patients with rheumatoid arthritis and the control group.

Sample	IL-17 pg/mL ± SE	Number	P-value / T-test	Sample
R. A	103.43 ± 29.17	100	P-value: 0.0001	T-test: 9.75
Control	60.12 ± 10.34	80		

Research found that plasma IL-17A levels were considerably greater in RA patients compared to healthy individuals ($p < 0.0001$). This confirms Serbian results [20], Taiwanese [21, 22], popu- lations from [23] and [10, 24] also performed a meta-analysis that proved the correlation between RA and high IL-17 levels in the blood. Using a ROC curve, we found that the plasma IL-17 cut-off was 18.25 pg/mL, which produced a 61.7% sensitivity and 100% specificity. Almost the same [10], another study with 108 RA patients and 202 healthy controls from Tunisia revealed. In that study, a serum IL-17 cut-off value of 23 pg/mL demonstrated a sensitivity of 55.56% and a specificity of 100%. On the other hand, several autoimmune diseases were shown to have elevated IL-17 levels [25].

Research conducted in the 1990s demonstrated that the joints of patients with RA exhib- ited elevated IL-17 expression compared to healthy individuals. [26, 27] have documented elevated serum levels of IL-17A in RA. Additionally, the peripheral blood of RA patients exhibited elevated expression of IL-17RA, and their levels were detected locally in the synovium of RA patients [28]. By inducing the synthesis of many cytokines, chemokines, antimicrobial peptides, and matrix met- alloproteinases in fibroblasts, endothelial cells, and epithelial cells, the IL-17A signalling pathway participates in inflammation and infection defence [29].

3.4 Genotype and Allele Frequency

According to the Hardy-Weinberg equilibrium theory, the genotype distribution of the rs2275913 polymorphism is visible in both the RA group (df=1, $\chi2 = 0.27$, P=0.613) and the control group (df=1, $\chi2 = 0.003$, P=0.949). The results of genotype frequency in RA showed (GG, 41.25%; AA, 13.75%; GA, 45.00%) was effectively different from that of the control group (GG, 50%; AA, 10%; GA, 40%) ($\chi2 = 8.466$, df=2, P=0.014).

Table 4 demonstrates that the prevalence of AA homozygotes in the RA group was substan- tially greater than in the control group (13.75% compared to 10%). This resulted in a 3.73-fold increased risk for RA, with an OR of 3.73 (95% CI: 1.27 - 4.55, P=0.008). On the other hand, the heterozygous GA genotype (P=0.113) was not notably linked. Furthermore, the risk of RA was much more significant in 1.78 (OR=1.78, 95% CI: 1.17 - 2.04; P=0.039) than in the mutant A allele.

Table 4: Genotype and allele frequency in patients with rheumatoid arthritis and the control group

IL17A Genotypes/alleles	CAD group n (%)	Control group n (%)	OR (95% CI)	P
GG	33 (41.25)	40 (50.00)	Ref.	-
GA	36 (45.00)	32 (40.00)	2.01 (0.94 - 2.11)	0.113
AA	11 (13.75)	8 (10.00)	3.72 (1.27 - 4.55)	0.008
G	102 (63.75)	116 (72.50)	Ref.	-
A	58 (36.25)	44 (27.50)	1.78 (1.17 - 2.04)	0.039

DISCUSSION

In this research, no meaningful correlation was identified between IL-17A rs2275913 and susceptibility to disease, p = 0.92. This finding validated an earlier report concerning the Tunisian population [10]. Once more, the majority of published research was conducted in Algeria [30]. The absence of a correlation between IL-17A rs2275913 and RA risk was emphasized in populations from Poland [31–33]. However, two investigations were conducted in [34] and Norway [35]. Effects of TNF and IL17 Gene Variations on Spondyloarthritis Immunopathogenesis in a Brazilian Co- hort, Independent of HLA-B27. Researchers discovered that rs2275913 polymorphism increases the risk of RA (Mediators of Inflammation, 2018(1), 1395823). The IL-17A*G allele in Norwegian individuals was reported in a 2009 study by Nordang et al., with an odds ratio (OR) of 1.17 and a 95% confidence interval (CI) of 1.02-1.34. Brazilian research linked the IL-17*G/G genotype to a modest risk of RA, with an odds ratio of 3.18. A meta-analysis by Lee et al. (2016) found that the IL-17A*A allele had little protective impact against RA incidence (OR = 0.866; 95% CI = 0.794–0.944).

Norwegian research [35] was the most significant in a meta-analysis involving 950 RA patients and 933 healthy controls. The risk of RA susceptibility associated with the IL-17A rs2275913 G allele may be negligible, indicating that most published research, including the current study, has not found a correlation between the IL-17A polymorphism and RA activity.
Ouled [10] observed that methotrexate helped patients with a single IL-17A*A allele. The IL- 17*G/G genotype was most active in anti-TNF therapy in Polish research (Kohno et al., 2008). The promoter of the IL-17A gene has the rs2275913 variant at -197. Although its functional effect is unclear, research shows it may boost promoter activity and cytokine production.

Research carried out by scientists indicated that the IL-17A rs2275913 SNP is notably linked to the risk of RA in Pakistan [36]. Chinese [33], Norwegian, New Zealander, Brazilian [37], and groups. The GG genotype of the IL-17A rs2275913 gene variant in the Polish population was associated with less effective anti-TNF therapy responses [38]. Due to this polymorphism, the Tunisian population showed improved patient responses to biological therapies and MTX treatments [39].

Research suggests that IL17A and IL17F may be genes linked to RA susceptibility, clinical disease manifestation, and therapy reactions. Nevertheless, broader studies involving a more varied range of ethnic groups ought to be conducted to ascertain whether these polymorphisms are associated with RA pathology, progression, and treatment response [40].

CONCLUSION

This study illustrated that the genotype and allele frequency of IL-17 A gene polymorphisms differ significantly between controls and RA patients. This suggests a potential correlation with RA susceptibility in the Iraqi population.

6. Importance of Study

The importance of the study lies in the possibility of using some immunological parameters, such as interleukin 17, as an indicator of the presence of rheumatoid arthritis, in addition to conducting genetic variation tests because of their relationship to rheumatoid arthritis.

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Conflicts of Interest:

The authors declare no conflict of interest.

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