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Review Article

The Association of Genetic Polymorphisms in Tumor Necrosis Factor-Alpha and Interleukins with Disease Severity or Response to Biological Therapy in Iraqi Rheumatoid Arthritis Patients: A Narrative Review

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Abstract

Background: Tumor necrosis factor-alpha (TNF-α) and interleukins play important roles in the pathogenesis of rheumatoid arthritis (RA). Genetic research has been employed to find many of the missing connections between genetic risk variations and causal genetic components. ***Objective***: The goal of this study is to look at the genetic variations of TNF-α and interleukins in Iraqi RA patients and see how they relate to disease severity or response to biological therapy. ***Method***: Using specific keywords, the authors conducted a systematic and comprehensive search to identify relevant Iraqi studies examining the genetic variations of TNF-α and interleukins in Iraqi RA patients and how they relate to disease severity or response to biological therapy. ***Results***: Thirteen studies have looked at TNF-α and interleukin genetic polymorphisms in Iraqi RA patients. Only the IL-2, IL-4, IL-6, IL-17, and IL-23 receptor gene polymorphisms were explored for interleukins; however, the results of studies indicate no association between genetic polymorphism and the severity of RA. Very few researchers examine the correlation between genetic variation and TNF-α inhibitor responsiveness. Numerous studies have been conducted to investigate the genetic variations of the TNF-α promoter. The -308 G/A region in the promotor region was the most studied location.

Keywords: Rheumatoid arthritis, Genetic polymorphism, Tumor necrosis factor-alpha, Interleukins, Iraqi patients

العلاقة بين تعدد الأشكال الوراثية في عامل نخر الورم ألفا والإنترلوكينات مع شدة المرض أو الاستجابة للعلاج البيولوجي في مرضى التهاب المفاصل الروماتويدي العراقيين: مراجعة سردية

الخلاصة

الخلفية: يلعب عامل نخر الورم ألفا (TNF-α) والإنترلوكينات أدوارا مهمة في التسبب في التهاب المفاصل الرثوي. تم استخدام الأبحاث الجينية للعثور على العديد من الروابط المفقودة بين اختلافات المخاطر الجينية والمكونات الجينية السببية. **الهدف**: الهدف من هذه الدراسة هو النظر في الاختلافات الجينية لعامل TNF-α والإنترلوكينات في مرضى التهاب المفاصل الروماتويدي العراقيين ومعرفة كيفية ارتباطها بشدة المرض أو الاستجابة للعلاج البيولوجي. **الطريقة**: باستخدام كلمات رئيسية محددة، أجرى المؤلفون بحثا منهجيا وشاملا لتحديد الدراسات العراقية ذات الصلة التي تبحث في الاختلافات الجينية ل TNF-α والإنترلوكينات في مرضى التهاب المفاصل الروماتويدي العراقيين وكيفية ارتباطها بشدة المرض أو الاستجابة للعلاج البيولوجي. **النتائج**: أجريت ثلاث عشرة دراسة تتعلق بتعدد الأشكال الجينية التي تخص TNF-α والإنترلوكين في مرضى التهاب المفاصل الرثوي العراقيين.تم استكشاف تعدد أشكال جينات مستقبلات IL-2 و IL-4 و IL-6 و IL-17 و IL-23 فقط للإنترلوكينات. ومع ذلك، تشير نتائج الدراسات إلى عدم وجود ارتباط بين تعدد الأشكال الوراثية وشدة التهاب المفاصل الرثوي. يدرس عدد قليل جدا من الباحثين العلاقة بين التباين الجيني واستجابة مثبطات TNF-α وتم إجراء العديد من الدراسات للتحقيق في الاختلافات الجينية لمروج TNF-α وكانت المنطقة -308 G/A في منطقة التحفيز هي الموقع الأكثر دراسة.

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INTRODUCTION

Rheumatoid arthritis (RA) is caused by a variety of variables, although the exact etiology is still unknown. It was found that disease activity is influenced by a person's genetic make-up, environment, and dysregulated immunological responses [1]. Interleukin (IL)-1, IL-2, IL-6, IL-17, interferon-gamma (INF-γ), and tumor necrosis factor-alpha (TNF-α) are pro-inflammatory cytokines that are expressed more frequently in RA illness. In fact, the synovial fluid of RA patients contains the majority of these cytokines [2]. An inducible cytokine with a wide range of pro-inflammatory and immunostimulatory functions is tumor necrosis factor-alpha. In the pathophysiology of RA, this cytokine is crucial. As the condition progresses, it starts the inflammatory response that results in swollen joints and subsequent bone destruction. At least ten separate genetic areas may be involved in the development of RA, and variations in clinical manifestation and therapeutic response may result from these genetic variations [3]. While cytokine genes, including as TNF-α, IL-1, IL-6, and IL-10, are crucial mediators of the inflammatory response and play a crucial part in the pathophysiology of joint inflammation and RA damage, the majority of the genes associated with RA propensity are located within the HLA-DR locus [4]. By increasing the production of TNF-α, polymorphisms in the TNF-α gene, such as (-1031 T/C, -863 C/A, -857 C/T, or +1304 G/A, can increase RA susceptibility [5,6]. Using epigenetic research, high-resolution mapping of open chromatin, chromosomal conformation technologies, and other techniques, many of the gaps between genetic risk variations and causal genetic components can now be filled in, furthering our understanding of RA genetics [7]. The association between various genotypes of many variations and the propensity to be non-responsive to biological therapy or the severity of RA disease has been the subject of numerous research [8-10]. However, the majority of these studies' conclusions were contradictory [8-10], and the only striking and statistically supported finding regarding the reasons for the inadequate response to TNF-α blockers is the current smoking status of RA patients [11-13]. In this review, we will look at the distribution of genetic variants in tumor necrosis factor-alpha and interleukins in Iraqi rheumatoid arthritis patients and how these polymorphisms relate to the severity of the disease or the effectiveness of biological therapy.

METHODS

Using particular keywords, a thorough and methodical search of the PubMed, Google Scholar, and ResearchGate databases was carried out using key words like "rheumatoid arthritis," "genetic polymorphism," "Iraqi patients," "interleukin," and "tumor necrosis factor alpha". The results of our preliminary search came back with fifteen separate studies. After that, two authors went through all of the articles, read their titles and abstracts, and eliminated two of the studies that weren't relevant. Due to the fact that we were unable to correctly categorize the research based on the titles and abstracts, we decided to conduct a full-text verification. During the process of selecting relevant publications for the study, any disagreements that arose were discussed, and then they were resolved by reaching a consensus.

Inclusion and exclusion criteria

The primary search results were imported into Mendeley, and publications were evaluated using the following criteria: 1) all studies investigating the link between TNF-α or interleukin gene polymorphisms and RA; 2) articles with sufficient data to extract; 3) publications that revealed genotype or allele frequencies in RA patients. Duplicates, reviews, meta-analyses, case studies, book chapters, letters to the editor, and conference abstracts were not included.

Data extraction and quality assessment

All of the essential data were extracted in accordance with the standardized extraction checklist, which included the name of the first author, the journal and publication year, the city, the mean or range of age, the method of genotyping, and the genotype counts in both the case and control groups. In order to improve the reliability of our findings, each of the three authors extracted the data on their own, and any discrepancies were ironed out through consensus.

RESULTS

The thirteen papers that qualify for this review are listed in Table 1 by their characteristics. The publications were released between 2015 and 2021, and overall, they had outstanding methodological quality. In patients with RA, the homozygous AA genotype was more common and significant. The heterozygous GA genotype was present in 45.24% of RA patients and 82.33% of controls, whereas fewer patients and controls had the GG genotype [14]. Furthermore, a poor response to etanercept has been associated with the -863CC genotype, either alone or in conjunction with -857CC. The response to etanercept was greatly enhanced by the GG genotype of -308 G/A and the AA genotype of -863C/A [8]. The tendency to not respond to etanercept was not correlated with the polymorphisms in the TNF-α promoter region at -376G/A, -806 C/T, and -1031T/C [15]. The TNF-α 308 SNP is not correlated with RA in the Iraqi population, according to another study [16].

Table 1: Characteristics of included Iraqi studies

Authors	Aims	Genotypes proportion	site	Duration	Medication of RA	Study design
Dhabaan [14]	Examine the association between the TNF-α-308 G/A polymorphism and RA in 42 Iraqi patients.	-308G/A, GG =11.90, GA = 45.24, AA = 42.86.	Baghdad, Iraq	2016–2017	Not specified	Case-control
Mohammed *et al*.[9]	Evaluate the association between polymorphisms in the promoter region of the TNF-α gene at locations -308G/A, -857C/T, and -863 C/A with the tendency of being non-responder to etanercept in 80 RA patients	-308 GG = 76.25, GA = 16.25, AA = 7.5 -857, CC =78.75, CA = 21.25, -863 CC = 68.75, CA = 18.75, AA = 12.25.	Baghdad. Iraq	October 2020 to August 2021,	Etanercept	Cross-sectional
Mohammed *et al*. [15]	Investigate presence of genetic polymorphism in the TNF-α gene promoter region at locations -376 G/A (rs1800750), -806 C/T (rs4248158), and -1031 T/C (rs1799964) of 80 patients affects RA patient's tendency to be a non-responder to etanercept	- 376 (GG = 95, GA = 5) - 806 (CC = 90, CA = 10) -1031 (TT = 68.75, TC = 27.5, CC = 3.75).	Baghdad. Iraq	October 2020 to August 2021,	Etanercept	Cross-sectional
Mahmood *et al*. [16]	Evaluate the association between RA and a single nucleotide polymorphism (SNP) (rs1800629) -308 G/A in the promoter region of the TNF-α gene of 51 RA patients.	GG = 72.5%, GA = 15.7%, AA = 11.8%	Baghdad-Iraq	November 2015-June 2016.	Not specified	Cross-sectional
Hachim *et al.* [11]	To evaluate the role of TNF-α-308G>A polymorphism in 29 RA patients who lack response to infliximab.	The frequency of the A allele was 39.7% in RA patients; the G allele was 60.3% in RA patients; in controls, A and G alleles frequencies were 8.3% and 91.7% respectively.	Baghdad	May 2014 to January 2015	infliximab	Prospective
Al-Terehi *et al* [17]	Explore the TNF-α gene polymorphism in 44 patients suffering from RA.	GG = 5.55%; AA = 38.88; GA = 61.11%.	Hilla city, Iraq	2017	Not specified	Case-control study
AL-Samarraie *et al*. [18]	Evaluate the connection between polymorphism of the TNF-α and the site of the disease (-308G/A), and how it is connected to the RA in 100 patients	52% of patients had allele G, while 48% had allele A.	Salah Al-Din, Iraq	2019	Not specified	Case-control
Alanzy *et al*. [19]	Evaluate the association between TNF-α levels and the -308 G/A TNF-α promoter polymorphism in 45 RA patients.	GG = 60%, GA = 40% AA = 0%	Babylon, Iraq	August 2016-July 2017	Not specified	Case-control study
Ad'hiah *et al*. [20]	Study the gene expression and polymorphism of IL-4 in a sample of 51 Iraqi RA patients receiving etanercept therapy.	IL4 gene (rs2243250), CC=72.5, CT=25, and TT=2.	Baghdad, Iraq	Not specified	Etanercept	case-control study
Salih *et al*. [21]	Evaluate the association of IL-4 gene polymorphisms with RA in 50 Iraqi patients.	IL4-590C/T (rs11209032), CC = 40, CT=34, and TT=26.	Not specified	Not specified	Not specified	case-control study
Ad'hiah *et al*. [22]	Evaluate IL-6 gene expression and six SNPs (rs1800796 C/G, rs7802307 A/C/T, rs7802308 A/T, rs36215814 A/G, rs184229712 A/G, and rs867254801 C/G) in 50 Iraqi RA patients treated with etanercept.	rs1800796, CC= 92.1, CG= 5.9, GG= 2.0, rs7802307, AA= 62.8, AT= 27.5, TT= 9.8. rs7802308, AA= 27.5, AT= 49.0, TT= 23.5. rs36215814, GG= 84.3, GA= 15.7. rs184229712, AA= 9.8, AG= 45.1, GG= 45.1. rs867254801, GG= 35.3, GA= 56.9, AA= 7.8.	Baghdad. Iraq	November 2015–June 2016	Etanercept	Case-control Study
Mahmood *et al*. [23]	Evaluate gene expression of IL-17A in 51 Iraqi patients with RA, with emphasis on clinical, pathological, and lab characteristics, and SNPs in and their connection with the disease.	IL-17A gene (rs3819025 SNP), AA= 62.7, AG= 23.5, GG= 13.7	Baghdad, Iraq	November 2015-June 2016	Etanercept	Case-control Study
Altamemi *et al*. [24]	Determine the role of IL-23R 11209026 gene polymorphism in RA vulnerability	IL-23R (rs11209026), AA= 77.5, AG= 17.5, GG= 5.	AL-Diwaniyah, Iraq	January 2017-May 2017	Not specified	Case-control Study

While Al-Terehi *et al*. (2017) showed the variation in TNF-α genotype linked with RA in Iraqi patients [17], Hachim *et al*. (2017) reported a correlation between the TNF-α-308 polymorphism and the responsiveness to treatment with infliximab [11]. Additionally, Al-Samarraie *et al*. (2020) found that the G allele was much more common in the community of RA patients from Iraq [18]. Alanzy *et al*. (2020) shown in a study done in Babylon province that the TNF-α (-308G/A) gene polymorphism was not related to the RA risk factor [19]. According to Ad'hiah *et al*. (2018) [20], the SNP genotypes did not impact the expression of the IL4 gene, and allele and genotype frequencies for the IL-4 gene SNP did not differ substantially between RA patients and controls. Salih stated in 2018 that there were notable differences in the genotype distributions and allele frequencies of the IL-4-590 C/T polymorphisms between RA patients and healthy people. There were variations in IL-4-590 genotypes that were statistically significant. In RA patients, there were noticeably greater frequencies of the T allele on IL-4-590 [21]. Ad'hiah *et al*. (2018) noted differences in the allele and genotype frequencies of four SNPs (rs1800796, rs7802307, rs184229712, and rs867254801) between patients and controls, but no differences were found for rs7802308 and rs36215814 [22]. The allele and genotype frequencies for the SNP rs8193038 did not substantially differ between RA patients and controls, according to a 2019 study by Mahmood *et al*. [23]. The second SNP (rs3819025) was found to have three genotypes (AA, AG, and GG). Only 13.7% of patients were found to have the homozygous genotype of the mutant allele (GG) among these genotypes, while no controls had this genotype [23]. Altamemi *et al*. (2018) demonstrated that there was no correlation between rs11209026 gene polymorphism and RA susceptibility in the Iraqi population with regard to IL-23 R gene polymorphism [24].

Pharmacogenomics of Interleukins in RA Pathology

Other forms of pro-inflammatory mediators that influence the course of RA include interleukin (IL)-1, IL-2, IL-4, IL-6, and IL-17. Cytokines are a big family that encompasses all of these pro-inflammatory mediators. Every single one of these families has a direct impact on the disease's development as well as its prognosis [25].

Interleukine-2 gene polymorphism

Because it promotes T-cell proliferation, increases natural killer activity, and improves anti-tumor immunity, interleukin-2 is thought to be a key pro-inflammatory mediator [26,27]. As a cytokine necessary for Treg cell formation, interleukin-2 stimulates regulatory T (Treg) cell proliferation to limit the inflammatory response and maintain immunological tolerance in addition to activating traditional T cells to boost its pleiotropic action and the immune response [27-29]. In a study conducted on Iraqi RA patients recruited from Baghdad city, the cytokine gene (IL-2) polymorphism was investigated. The findings show that RA risk was decreased in patients with the C allele in C/C and the A allele in A/A. Patients with the A/C genotype, however, were more likely to get the illness [30]. This investigation found a significant difference between the mutant homozygous A/A and the mutant heterozygous A/C alleles of the IL-2 gene among RA patients in the Baghdad community [30]. Chinese RA patients were the control group in a 2007 study by Lee *et al*., and they discovered no differences between them and the RA patients [31]. The IL-2 TG:GG cytokine diplotype was found to be positively associated with RA in a study on Turkish individuals with the disease published in 2020. On the other hand, no meaningfully adverse link was found [32].

Interleukine-4 gene polymorphism

Another cytokine with high amounts in RA patients' serum is IL-4. The first B-cell pleiotropic cytokine to be identified, IL-4 promotes T cell growth and B cell synthesis of antibodies. It is important for the immunological system [33,34]. The IL-4 gene is strongly expressed compared to the control group, according to the study conducted by Ad'hiah *et al*. (2018) [20] on Iraqi patients with RA recruited from Baghdad Teaching Hospital. However, compared to male patients, this rise was noticeably more pronounced in female RA patients. Another study that included 40 healthy control groups and 50 RA patients from the Iraqi community discovered that the genotype distributions and allele frequencies of the IL-4-590 C/TAA polymorphism in RA patients were significantly different from those in healthy individuals. Statistically significant variations in IL-4-590A genotypes were found. Patients with RA had significantly higher T allele frequencies on the IL-4-590A [21]. The outcomes of the two earlier investigations are consistent with other research that found that South Indian RA patients had much higher serum levels of IL-4. Additionally, it was noted that patients' *IL4* gene expression was higher than that of healthy controls', but this difference was not statistically significant [35]. According to the study by Ad'hiah *et al*. [20], the level of IL-4 was found to be negatively linked with DAS-28; as the DAS-28 value rose, IL-4 decreased. The same study discovered that seronegative individuals had larger amounts of cytokines than seropositive patients, according to RF findings. Individuals who were CRP seropositive displayed higher levels of IL-4 than patients who were CRP seronegative. Strongly seropositive patients had the greatest levels of IL-4 in the same trial, followed by weakly and moderately seropositive patients [20]. The researchers divided the RA patients according to ACCP antibodies. The findings of earlier research that looked at the overall functional role of IL-4 in

the pathogenesis of RA as an autoimmune disease refuted the idea that IL-4 plays a general role and is not responsible for the negative effects of the disease [36]. Additionally, IL-4 is thought to have anti-inflammatory effects in cases of autoimmunity brought on by aberrant immunological processes. These illnesses, as shown in RA patients, are dependent on the activation of monocytes and Th1 cells, which then release pro-inflammatory cytokines (IL-1, IL-6, IL-8, IL-12, and TNF-α) to exert their effects [36]. It's also interesting to note that very low quantities of IL-4 have been reported in the synovial fluid of RA patients; IL-4 synthesis by cultured cells from the synovium of patients has either not been observed or has been produced at low levels [36].

Interleukine-6 gene polymorphism

In response to an inflammatory stimulus, interleukin-6 is produced locally and can cause systemic symptoms away from the site of inflammation. There is a significant increase in the variety of cell types that respond to IL-6 as a result of its distinct signaling mechanism, which includes both classical and trans-signaling routes. This pleiotropic cytokine plays a significant role in the pathophysiology of RA and is responsible for several extra-articular symptoms that are associated with the condition [37]. Patients with rheumatoid arthritis (RA) had higher levels of interleukin-6 gene expression in their serum and synovial fluid, and this increase was positively connected with disease activity (DAS-28) [22]. Additionally, several studies show a connection between this cytokine and regional inflammation and joint degeneration; it affects osteoclast activity, macrophage function, and T and B lymphocyte activity [38,39]. The impact of IL-6 polymorphisms (rs36215814 and rs184229712) to RA risk in Iraqi RA patients was assessed in a study by Hussain *et al*. [40]. The findings showed that the frequency of the heterozygous mutant genotype AG was substantially higher in RA patients than in controls for the IL6 polymorphism, rs184229712. In contrast, although the difference was not statistically significant, the control group (68%) had a higher prevalence of the AA genotype than did the RA group (40%). The GG allele had the lowest frequency, and there was no discernible difference between the control (5%) and RA (12%) groups. Numerous investigations, including the Iraqi study, discovered that RA patients had considerably greater levels of the GG genotype of the IL-6 SNP rs184229712 (A/G) compared to the control group. Additionally, the AG genotype of the IL6 rs184229712 SNP was discovered to be substantially related with increased IL-6 gene expression compared to the GG genotype; it is postulated that this SNP affects IL6 gene expression and, as a result, its blood level in RA patients [41-43]. In addition, genotype frequencies of the IL-6 polymorphism rs184229712 were examined using dominant, recessive, and additive genetic models in a study conducted by Hussain *et al*. The rs184229712 polymorphism was strongly connected to an elevated incidence of RA under the dominant and additive genetic models [40]. Hussain *et al*. (2021) discovered that the heterozygous GA mutant genotype was substantially more common in RA patients (39%) compared to controls (24%) for the IL-6 polymorphism, rs36215814. Additionally, RA patients had a considerably higher frequency of the A allele than did healthy controls [40]. The GG and AA genotypes cannot be distinguished from one another. The rs36215814 polymorphism was strongly related with a greater incidence of RA in both the dominant and additive genetic models. The IL-6 GG haplotype was positively related with RA, according to a study conducted in 2020 among Turkish patients with RA [32].

Interleukin-17 gene polymorphism

Locally acting on synoviocytes and osteoclasts in rheumatoid arthritis, IL-17A strengthens the connection between synoviocytes and joint deterioration [44]. In RA patients, IL-17 expression was found to be increased by Mahmood *et al*. The study also divided the patients into groups based on the amounts of DAS-28 and ACCP antibodies in their bodies. The group of patients with a low DAS-28 score had the lowest mean value of IL-17 expression, whereas the group of patients with a high DAS-28 score had the greatest value, according to Mahmood *et al*. Additionally, individuals with weak positive results for ACCP antibodies had the greatest mean, whereas those with moderate and strong positive results had lower significant means [23]. Only two SNPs (rs8193038 and rs3819025) showed polymorphic allele frequencies, according to Mahmood *et al*. Both the genotype frequency and allele frequency of RA patients and controls were similar for the rs8193038 SNP. For the second SNP (rs3819025), three genotypes (AA, AG, and GG) were found in RA patients, but only two genotypes (AA and AG) were found in controls [23]. According to the study, only 13.7% of RA patients had the homozygous genotype of the mutant allele (GG) among these genotypes and alleles. None of the controls, however, have this genotype. Additionally, it was shown that the G allele frequency was 12.2% higher in patients, whereas the A allele frequency drastically decreased by 87.8% [23]. The findings of the study are comparable to those of a study carried out in Egypt, which revealed that there was no discernible difference in IL-17A (197A/G; rs2275913) levels between the RA patients and the control group [45]. Forty RA sufferers from Iraq who visited the consultant clinic for rheumatology at Al-Diwaniyah Teaching Hospital were the subjects of a study by Altamemi *et al*. (2017). The findings showed that RA patients had a significantly greater value than the control group. Additionally, the link between disease severity and IL-17 was found when the expression

levels of IL-13 and IL-17 were compared with each other [24].

IL-23R gene polymorphism

Rheumatoid arthritis risk may rise due to the increased production of IL-23R that is linked to particular SNP alleles in its gene. A putative mechanism for the onset of rheumatoid arthritis, the IL-23/Th17 signaling pathway, which contains genes that generate IL-23/IL-23R, IL-17A, and IL-17F, may also play a role in disease susceptibility and progression [46]. Altamemi *et al.* (2017) investigated the relationship between RA in Iraqi patients and the rs11209026 SNP in the IL-23R gene. The frequency of the AA, AG, and GG genotypes in the patients was not significantly different from that of the controls, according to allele and genotype frequencies [24]. Furthermore, the rs11209026 gene polymorphism was not found to be a risk factor for RA by Altamemi *et al.* and there was no statistically significant connection between it with RA susceptibility in Iraqi individuals [24]. The findings of the Iraqi study agreed with those of Kubik *et al.* investigation regarding the association between the IL-23R (rs11209026) gene and RA susceptibility in Polish individuals with RA [47]. However, relatively recent meta-analyses found that additional IL-23R gene variations, such as IL-23R rs134315, rs10489629, and rs7517847, may be connected to the onset of RA in European RA patients [48].

TNF-α Gene Polymorphism in Rheumatoid Arthritis

One of the primary mediators of joint inflammation in RA is regarded as tumor necrosis factor-alpha. As it stimulates osteoclast (OC)-mediated bone resorption, several experimental studies have shown that it plays a substantial role in local joint injury and systemic bone loss [4,5]. By directly encouraging OC development in bone marrow macrophages exposed to permissible levels of RANK-ligand (RANKL), TNF-α promotes OC activity [49]. By identifying genetic characteristics that contribute to a lack of response to or toxicities from TNF-α inhibitors, pharmacogenetics has the potential to increase therapeutic effectiveness. TNF-α inhibitors have been found to be successful in treating patients with inflammatory or immune-mediated disorders, however a sizable portion of patients fail to experience a positive clinical response. But the factors that affect a drug's effectiveness and toxicity are still mostly unknown. Because of this, picking patients who will benefit from TNF-α inhibitors is still a lottery [50-52]. Pharmacogenetics presents the potential of being able to anticipate therapeutic efficacy and adverse drug events in addition to being able to explain inter-individual heterogeneity in drug response. Even while shared epitope (SE) and other genetic susceptibility indicators exist, the understanding that variation in response to TNF-inhibitor treatment may be related to genetic features has prompted research into genetic markers as possible predictors of response to treatment. It is still being investigated whether immune response-related protein-coding genes can accurately predict TNF-α inhibitor responses. However, a number of genetic variations in the TNF-LTa area have been examined. The obvious options for regulating TNF-α inhibitor reactions are TNF-α gene loci. SNPs in the TNF-α promoter gene positions -308, -238, and -857 as well as the TNF-α receptor gene sites -676 and -196 have all been found to be polymorphic portions of the TNF-α locus and have been studied [53]. There is no question that the TNF-α gene loci can affect how the body reacts to TNF-α inhibitors. Many polymorphic areas of the TNF-α locus have been discovered and investigated for their potential as markers for TNF-α inhibitor response, including SNPs at locations 308, 238, and 857 of the TNF-α promoter genes and 676 and 196 of the TNF-α receptor genes. According to a meta-analysis of earlier research, patients homozygous for the G allele respond better to anti-TNF-α therapy than those who carry the A allele at TNF-α-308 [54]. Numerous studies conducted in Iraq [9,11,14,16,18,19] on the genotype distribution for -308 G/A found that the GG genotype predominated in nearly three-quarters of the population, followed by heterozygote GA and homozygote AA. Additionally, whereas the A allele was present in a minor proportion of individuals, the G allele was detected in the majority of RA patients. A study by Azizi *et al.* carried out in Iran likewise found that genotype GG had the highest prevalence in RA, correlating with the results of the investigations carried out in Iraq. In contrast, both the RA and control groups had the lowest frequencies of the AA genotype [25]. Additionally, the findings of the Iraqi study were comparable to those reported by Ates *et al.* [54], who carried out research in Turkey, where 96% of the case and control groups had the GG genotype frequency and neither group had the AA genotype. The TNF-α gene promoter region SNP at position -308 has drawn the most interest as a potential genetic marker for TNF-α inhibitor response. The TNF-α-308GG genotype is often associated with a stronger response to TNF-α inhibitor therapy than the TNF-α-308AA polymorphism, according to several international research [55-58]. The availability of the GA and AA genotypes of the -308G/A polymorphism did not, however, differ significantly between responsive and non-responsive groups in a research by Mohammed *et al.* [10]. They evaluate a sample of Iraqi RA patients revealed that TNF-αRII 196M/R transfectants have been linked to increased production of IL-6, which contributes to the pathogenesis of RA in that country [10]. This result is in line with Aminikhoo *et al.* hypothesis that the existence of TFRII 196 M/R is associated with the diagnosis and prognosis of RA [58]. Patients with rheumatoid arthritis who carry the T allele of the

TNF-α-857C/T SNP respond better to etanercept therapy than do patients who carry the C allele, suggesting that, if the results are verified, this SNP could be a helpful genetic marker for anticipating responses. TNF-α-863C/A was significantly correlated with RA susceptibility in Thai RA patients, according to Lee *et al*. [31] and their research. The CC and CT genotypes were equally distributed between responsive and non-responsive patients, according to a research in Iraq by Mohammed *et al*. [10], with no statistically significant difference between the two groups and no correlation to etanercept responsiveness. This correlation was not supported by subsequent investigations, the findings of which revealed a tenuous correlation in various population studies [59-61]. According to an Iraqi study [15] on the prevalence of -1031T/C genotypes, more than 68% of patients had the TT genotype whereas just 3.75% of patients have the CC genotype. However, no statistically significant link between etanercept responsiveness and the -1031T/C polymorphism was found by the analysis. It's interesting to note that no prior studies have examined how 1031T/C affects RA patients' responsiveness to etanercept [15]. The TNF-α-376G/A SNPs may have functional significance and affect TNF-α gene expression levels, even though numerous experimental studies have been carried out to examine the relationship between TNF-α polymorphisms and its expression as well as the mechanisms governing its expression in a variety of cell types and diseases [61,62,63]. The impact of the TNF-α-376 G/A polymorphism on increased susceptibility to RA is unknown because they haven't garnered much attention in RA patients [64,55]. According to Mohammed *et al* study in Iraq [15], 95% of patients had the genotype GG, 5% had the genotype GA, and there were no homozygotes for the genotype AA. The G allele was found in all people, while the A allele was only found in 5% of RA patients. However, the results are comparable to those of a Turkish study that examined the association between TNF-α-376 G/A polymorphisms and Behçet's illness in Turkish patients [64]. There are no comparable global investigations on RA. The results also matched those of an Iranian study [58] that examined 376 G/A TNF-α gene polymorphisms in celiac patients. The impact of the -308G/A polymorphism on TNF-α blocker responsiveness as well as the impact of these polymorphisms on heightened susceptibility to and severity of RA were examined in several studies [65-67]. Results showed no significant difference in the availability of GA and AA genotypes of the -308G/A polymorphism between responsive and non-responsive groups, in contrast to the study by Mohammed *et al*. [9]. The responsive group, however, had a considerably higher presence of the GG genotype. These results in RA patients from Iraq are in line with several studies showing that TNF-α-308GG genotype RA patients respond better to etanercept than individuals with other genotypes [66,67,68]. No correlation was seen between the TNF-α-806 C/T genotype in RA patients and non-response to etanercept in Mohammed *et al*. study. There is no comparative RA research to compare these findings to. A solitary Indian study, however, found no correlation between the -806C/T genotype and susceptibility to SLE disease [68].

Conclusion

The genetic polymorphism of TNF-α and interleukins in Iraqi RA patients has been the subject of only a few studies. For interleukins, only the IL-2, IL-4, IL-6, IL-17, and IL-23 R gene polymorphisms were investigated; however, the results of multiple studies (20) (22) (24) reveal no correlation between the genetic polymorphism and the severity of RA. Few researchers investigate the relationship between genetic variation and response to TNF-α inhibitors. Numerous research examines the genetic variants of the promoter rejoin for TNF-α. The -308 G/A in the promotor region was the most investigated site in TNF-α gene.

Conflict of interests

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