Reviews in Health Care 2013; 4(1): 29-53

Disease
Narrative review

The role of TNF-α and TNF-β gene polymorphisms in the pathogenesis of rheumatoid arthritis

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Abstract

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disorder of unknown etiology that affects the synovial membrane of multiple joints. The clinical presentation of RA may vary from mild to severe with excessive erosions of periarticular bone leading to the loss of functional capacity. Both genetic and environmental factors are important in the development of this disorder. The genetic contribution to susceptibility for RA is underlined by a three- to four-fold higher concordance percentage for clinically expressed disease in monozygotic twins compared to dizygotic twins. The severity and long term outcome of RA have also been related to various genetic factors. Tumor necrosis factor (TNF), a pro-inflammatory cytokine, is involved in the pathogenesis of a variety of autoimmune disorders, including RA. A large number of studies have been undertaken to determine the role of TNF-α promoter polymorphisms in the pathogenesis of RA. On the other hand few attempts have been made to identify the association between TNF-α (lymphotoxin-alfa) polymorphism and RA. In this narrative review of published literature, an attempt has been made to determine the association between TNF-α promoter polymorphisms at positions –308, –238, –489, –857, –863 and TNF-β at +252 with respect to susceptibility to and severity of RA, as well as response to drug therapy. In spite of intra- and inter-ethnic variations, analysis of data suggests a significant role of TNF-α/TNF-β polymorphisms in determining the susceptibility/severity of RA and responsiveness to anti-TNF drug therapy. The TNF gene polymorphisms may be an interesting target for novel strategies to prevent RA and/or in its early treatment. Further studies using larger samples are needed to pinpoint the regulatory polymorphisms or haplotypes and their effects on the development of certain manifestations in RA.

Keywords

Tumor necrosis factor (TNF); Rheumatoid arthritis; Polymorphism; Saudi

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Disclosure
The authors have no conflict of interests or financial disclosures.

Introduction

Rheumatoid arthritis (RA, MIM#180300) is a chronic inflammatory autoimmune disorder with a prevalence of around 1% in the world's most populations. RA occurs when the body's immune defenses attack the tissue in the joints, leading to pain and degeneration of the articular cartilage. Arthritis usually begins in the small joints of the hands and feet, spreading later to the larger joints. The inflamed joints lining or synovium extends and then erodes the articular cartilage and bone, causing joint deformity and progressive physical disability. Extra-articular features include nodules, pericarditis, pulmonary fibrosis, peripheral neuropathy, and amyloidosis. Besides RA disease, side effects of drugs used for its treatment may also increase mortality and morbidity, and as a result patients with RA have a shorter life expectancy than their healthy peers. Drugs used to limit the symptoms have limited effect and do not improve the long term prognosis. The results are reduced quality of life, loss of working capacity, and subsequent invalidity.

The etiological factors underlying RA are not yet fully understood. During active RA, inflammatory cells such as monocytes/macrophages, mast cells, T cells, and B cells infiltrate the synovial joints. The immune cells interact in a complex and intricate manner leading to the release of pro-inflammatory mediators [1]. Cytokines, a group of modulatory proteins or glycoproteins produced by a wide range of cells in response to a variety of stimuli, are important mediators and regulators of synovial inflammation [2]. Basal and cell-stimulated cytokine levels differ between individuals; both genetic and environmental influences have been shown to play a role in their variability [3]. High levels of pro-inflammatory cytokines including tumor necrosis factor-α (TNF-α), interleukin (IL)-1, and IL-17 are detectable in the joint fluids and synovium of RA patients. These pro-inflammatory mediators have been demonstrated to play a vital role in the initiation and development of RA [4,5]. Abundant expression of pro- and anti- inflammatory cytokines observed in the affected tissues and serum of RA patients clearly indicates the involvement of cytokines in the etiopathology of RA [6].

Multi-factorial origins have been suggested for RA, indicating that environmental factors as well as the contributions of several genes appear to play a role in the development of the disease. The genetic component is emphasized by a 3-4 fold higher concordance rate in monozygotic compared to dizygotic twins [7-9]. The severity and long term outcome of RA have also been related to various genetic factors. Linkage studies in RA families and genome wide screening in case control studies have identified a large number of validated genetic loci associated with RA [10-18]. HLA-DRB1 is a major genetic component of RA across ethnicities and is estimated to contribute to 30-50% of the total genetic risk [19,20]. However, the other risk loci identified to date show ethnic-specific patterns of disease association [18,21-33]. Several cytokine genes have been considered as likely candidates for influencing susceptibility or severity of RA. Polymorphisms in these cytokine genes have been reported to be associated with RA [5,34-38].

Role of TNF-α and TNF-β in the pathogenesis of RA

Tumor necrosis factor (TNF), a pro-inflammatory cytokine, has been shown to play a pivotal role in the pathogenesis of several autoimmune diseases including RA [6,39,40]. This is further underlined by the development of several anti-cytokine drugs in the treatment of RA. In addition to inflammatory tissue destruction, factors involved in tissue repair and necrosis or apoptosis are likely to be involved in erosive disease and may also codetermine disease susceptibility. Both TNF-α, produced mainly by monocytes and activated macrophages, and TNF-β, produced mainly by activated T cells, play important immunoregulatory roles in various diseases. The genes for TNF-α (OMIM 191160) and TNF-β, also known as lymphotoxin-α (LT-α, MIM 153440), show close linkage to the HLA class I (*HLA-B*)

Population/Group	Genotype/Allele	Suggested association with RA	Reference
Saudis	GG/G	Susceptibility to RA	[48]
Egyptian	GG/G	Susceptibility to RA	[58]
Egyptian	A	Severity of RA	[58]
Egyptian	AA	Susceptibility to RA	[59]
Egyptian	GG	Severity of RA	[59]
Tunisian	G<A polymorphism	No association	[60]
Turkish	G<A polymorphism	Severity of RA	[61]
Turkish	G<A polymorphism	No association	[62]
Iranian	G<A polymorphism	No association	[63]
Serbian	G<A polymorphism	No association	[64]
Portuguese	GA	Severity of RA	[65]
Portuguese	GA/AA	No association with JIA	[66]
Czech	A	No association	[61]
Czech	A	Severity of RA	[67]
German	G<A polymorphism	No association	[68]
German	G	Protective to JIA	[69]
Polish	G<A polymorphism	No association	[70]
Polish	G<A polymorphism	No association	[71]
Indian	A	Protective to RA	[6]
Taiwanese	A	Protective to RA	[72]
Taiwanese	G<A polymorphism	No association	[73]
Han Chinese	A	Protective to RA	[47]
Japanese	G	Susceptibility to RA	[74]
Hungarian	A	Susceptibility to RA	[75]
Chilean	A	Susceptibility to RA	[76]
Spanish	A	Susceptibility to RA	[77]
Spanish	A	Susceptibility to RA	[78]
Spanish	G<A polymorphism	Severity of RA	[79]
Spanish	G<A polymorphism	No association with severity	[80]
Finnish	GG	Susceptibility	[81]
Swedish	G	Susceptibility to RA	[82]
Dutch	G<A polymorphism	No association	[83]
Dutch	A	Associated with severity	[84]
Caucasian	A	Susceptibility to RA	[85]
Caucasian	G<A polymorphism	No association	[86]
Caucasian	A	Susceptibility to RA	[87]
Caucasian	GG	No association	[88]
Caucasian	G<A polymorphism	No association	[89]
Mexican	A	Susceptibility to RA	[24]
Mexican	A	Susceptibility to RA	[78]
Mexican	A	Susceptibility to JRA	[90]
American	G<A polymorphism	Severity of RA	[46]
Slovanian	A	Low severity of RA	[91]
Latin American	G<A polymorphism	Susceptibility to RA	[92]
European	G<A polymorphism	No association	[92]
Several populations	A	Susceptibility to RA	[93]

Table I. Association of TNF-α –308 polymorphism in etiopathogenesis of RA in various populations

JIA = juvenile idiopathic arthritis; JRA = juvenile rheumatoid arthritis; RA = rheumatoid arthritis

and class II (*HLA-DR*) genes. TNF-α and TNF-β are closely related cytokines that share 30% amino acid residues and use the same cell surface receptor [41]. Nedwin et al. [42] reported that the TNF-α and TNF-β genes are located in tandem on chromosome 6 (chromosome 6p21.1-6p21.3). Studies on monozygotic twins and their first-degree relatives, using *ex vivo* endotoxin stimulated whole blood samples, have provided evidence that 60% of variation in the production capacity of TNF-α appears to be genetically determined [43]. Several polymorphisms within the promoter region of TNF-α and the intron 1 polymorphism of TNF-β, in particular, have been associated with altered levels of circulating TNF-α [44,45].

TNF-α –308 polymorphism and RA

The search for genetic heterogeneity within the TNF-α gene has disclosed several polymorphisms in the promoter region. TNF-α promoter polymorphisms have been widely studied as a possible risk factor for the onset, progression, and severity of RA. The review of the literature suggests that polymorphisms in TNF-α promoter such as TNF-α G308A (rs1800629), TNF-α G238A (rs361525), TNF-α G376A (rs3093659), TNF-α G489A (rs180061), TNF-α T857C (rs1799724), and TNF-α A863C (rs1800630) might be involved in the pathogenesis of RA.

Among all the polymorphisms of TNF-α gene identified by Polymerase Chain Reaction-Single Strand Conformational Polymorphism (PCR-SSCP) analysis, TNF-α –308 polymorphism has been studied most and reported to be associated with several autoimmune diseases including RA [46-48]. The genetic variation on position –308 results in two allelic forms in which the presence of guanine (G) defines the common variant and the presence of adenine (A) defines the less common one. TNF-α –308A allele displays increased gene transcription as compared to the common allele G. It has been shown to produce 6-7 fold higher levels of TNF-α transcription [49-53].

TNF-α –308 polymorphism and susceptibility to RA

TNF-α –308 polymorphism is associated with elevated TNF levels, enhanced susceptibility, and poor prognosis in several diseases [54-57]. The narrative review of several studies undertaken to determine the association of TNF-α polymorphisms –308 and RA in different parts of the world is presented in Table I.

The results of the studies on association of TNF-α polymorphism with RA are inconsistent. The differences in findings have been attributed to variation in ethnicity, sample size and method of diagnosis [95-97]. Recently, we reported significantly lower frequency of –308A allele and higher frequency of –308G allele in Saudi RA patients as compared to healthy controls [48]. We concluded that –308A allele of TNF-α may exert a protective influence for the development of RA whereas allele G and genotype GG might be a risk factor among Saudi patients. Our findings on Saudi patients are supported by earlier reports on other ethnic groups, including Taiwan Chinese [72], Japanese [74], Swedish [82], Finish [81], Hungarian [75], Han population of Eastern China [47], Egyptian [58], and Indian [6].

Contrary to these findings, numerous investigations showed significantly higher frequency of allele A or genotype AA in RA patients as compared to control group suggesting that TNF-α –308A is a predisposing factor among Caucasian [85,87], Mexican [24,78,90], Spanish [77-79], American [46], Dutch [84], Egyptian [59], Portuguese [66], Czech [67], and Serbian population [64].

On the other hand, no significant association between TNF-α –308 polymorphism and RA susceptibility was observed in Taiwanese [73], Polish [70,71], Iranian [63], Turkish [61,62], European [92], Tunisian [60], Czech [61], German [68], Spanish [80], Chilean [76], and Caucasians [86,88,89]. The exact reason for such variations in the distribution of alleles and genotypes of TNF-α –308 polymorphism in RA patients in different ethnic groups is far from clear. These differences may be attributed to the eth-

nicity-related genetic makeup in different populations, which is evident from the highly significant variations in genotype data of TNF-α –308 polymorphism among the healthy subjects of various ethnicities (Table II). Lee et al. [92] also suggested that ethnicity has a significant impact on the genotype distribution of TNF-α –308 polymorphism in RA patients. RA is considered to be a complex disorder and its onset and severity are influenced by genetic as well as environmental factors. Hence, the gene-environment interaction might be responsible for the significant differences in the results of polymorphism association studies on RA patients from various ethnicities/geographical locations.

Population/ Group	Genotype Frequencies (%)			Reference
	GG	GA	AA	
Saudis	50.0	38.09	11.90	[48]
American	68.2	29.1	2.7	[98]
Australian	58.0	39.0	3.0	[99]
Chilean	83.1	16.3	0.6	[100]
Chilean	90	10	0	[76]
Chinese	85.6	13.3	1.1	[47]
Chinese	83.2	15.7	1.1	[101]
Czech	80.66	19.33	0.0	[67]
Danish	65.8	30.5	3.7	[102]
Dutch	56.6	38.6	4.5	[83]
English	59.6	37.4	3.0	[103]
Finnish	68.8	30.0	1.3	[81]
French	81.6	17.2	1.2	[104]
German	67.0	28.0	5.0	[105]
German	67.35	31.12	1.53	[69]
Iranian	96.7	3.3	0.0	[63]
Japanese	97.0	3.0	0.0	[106]
Macedonian	76.8	21.9	1.3	[107]
Mexican	91.4	8.6	0.0	[24]
Spanish	82.4	15.7	1.9	[79]
Swedish	56.5	40.5	3.0	[108]
Taiwanese	83.4	15.8	0.8	[73]
Turkish	82.79	17.21	0	[62]
West African	81.6	17.0	1.4	[109]

Table II. Genotype distribution of TNF-α –308 promoter polymorphism in different healthy groups

TNF-α –308 polymorphism and severity of RA

The –308A allele is associated with high levels of TNF-α, suggesting that a genetic predisposition to produce higher levels of TNF-α might contribute to subsequent development of erosions and radiographic damage. Significantly increased levels of TNF-α have been observed in arthritis synovial fluid [110], and inhibition of TNF-α using a TNF receptor fusion protein markedly improves skin and joint inflammation in RA patients [111]. The association of the alleles and genotypes of TNF-α –308 polymorphism has been reported with severity of RA in American, Mexican, and Czech populations [24,46,67].

Khanna et al. [46] found an association between TNF-α –308 polymorphism and progression of radiographic damage in American patients with early seropositive RA, and suggested that the association might be dependent on genetic variants in linkage disequilibrium with TNF-α –308A allele and DRB1*0301. Rodríguez-Carreón et al. [24] also found an association between TNF-α –308A allele and severity of RA in Mexicans which was independent from HLA-DR alleles. Nemec et al. [67] found no difference in the distribution of genotypes and alleles frequencies of TNF-α –308 between the Czech RA patient and control groups. However, on dividing the RA group according to the radiographical progression of disease, a significant difference in the distribution of genotypes was noticed, suggesting that GG genotype of TNF-α –308 polymorphism is associated with the severity of RA in Czech population. Wilson et al. [86] reported that RA patients with allele A tend to have an increased number of erosions. Vinasco et al. [79] did not find any correlation between RA and TNF-α –308 promoter polymorphism, but they found an increased frequency of nodulosis among patients with the allele A. The GA genotype of TNF –308 polymorphism has been reported to be associated with joint erosions in German polyarthritis patients [69]. Similarly, Rezaieyazdi et al. [63] also suggested that TNF-α –308 polymorphism may be associated with radiographic damage in Iranian RA patients.

Contrary to these, no significant association between erosive disease and TNF-α polymorphism was found in Turkish patients [62]. Absence of any association between the TNF-α polymorphism and clinical manifestations or severity of RA has also been reported by other investigators [48,70,86,112]. In a 5-year follow-up study on British polyarthritis patients no association between TNF-α promoter polymorphism and severity of radiographic erosions was observed [112]. A study on Polish RA patients also failed to show any correlation between TNF-α –308 polymorphism and radiological progression of the disease [70].

TNF-α –238 polymorphism and RA

The association between TNF-α G238A polymorphism and several inflammatory diseases including systemic lupus erythematosus [113], juvenile onset psoriasis, and psoriatic arthritis [114], scarring trachoma [109], and an alcoholic steatohepatitis has been reported. However, meta-analysis of the data on the role of TNF-α –238 polymorphism in RA has yielded inconclusive results (Table III).

Several studies showed significant association of allele G or genotype GG of TNF-α 238 polymorphism with RA susceptibility or severity [24,83,89,107,115-117], while others showed an association of allele A or genotype GA with susceptibility/severity of RA/JRA [69,90,118]. On the other hand, some studies showed no significant association of any allele/genotype of TNF-α 238 polymorphism with RA [47,61,62,68,72,78,79].

It has been shown that the variables like ethnicity, age, and gender might play a significant role. In a case-control study, a significant association was reported between the TNF –238GG genotype and earlier onset and severity of RA in Dutch population [83]. These investigators identified the TNF –238GG

Population/Group	Genotype/Allele	Suggested association with RA	Reference
Mexican	GG	Susceptibility to RA	[24]
Mexican	G<A polymorphism	No association	[78]
Mexican	GA	Association with JRA	[90]
Macedonian	A	Protective to RA	[107]
Italian	GG	Susceptibility to RA	[115]
German	A	Susceptibility to JIA	[69]
German	G<A polymorphism	No association with RA & JRA	[68]
Turkish	G<A polymorphism	No association with JIA	[61]
Turkish	G<A polymorphism	No association	[62]
Spanish	G<A polymorphism	No association	[79]
Dutch	GA	Protective to RA	[83]
Dutch	GG	Severity of RA	[116]
Caucasian	G	Susceptibility to JIA	[117]
Caucasian	GG	Susceptibility to RA	[89]
Chinese	G<A polymorphism	No association	[47]
Taiwanese	G<A polymorphism	No association with severity	[72]
Syrian	G<A polymorphism	Association with severity	[118]

Table III. Association of TNF-α –238 polymorphism in etiopathogenesis of RA in various populations

JIA = juvenile idiopathic arthritis; JRA = juvenile rheumatoid arthritis; RA = rheumatoid arthritis

Population/ Group	Genotype/Allele	Polymorphism	Suggested association with RA	Reference
Turkish	G<A polymorphism	TNF-α –376	No association	[62]
Taiwanese	G<A polymorphism	TNF-α –376	No association	[72]
Caucasian	G<A polymorphism	TNF-α –376	No association with JIA	[117]
Caucasian	G<A polymorphism	TNF-α –376	No association	[89]
Dutch	G<A polymorphism	TNF-α –376	No association	[83]
Dutch	GG	TNF-α +489	Susceptibility to RA	[34]
Italian	AA	TNF-α +489	Protective to RA	[115]
European	A	TNF-α +489	No association	[121]
Caucasian	A	TNF-α +489	Susceptibility to JIA	[117]
Canadian	A	TNF-α +489	Susceptibility to RA	[122]
German	C<T polymorphism	TNF-α –857	No association with RA/JRA	[68]
Caucasian	T	TNF-α –857	Susceptibility to RA in male	[85]
Caucasian	C<T polymorphism	TNF-α –857	No association with JIA	[117]
Caucasian	C<T polymorphism	TNF-α –857	No association	[89]
Chinese	C<T polymorphism	TNF-α –857	No association	[47]
Taiwanese	C<T polymorphism	TNF-α –857	No association	[72]
Japanese	T	TNF-α –857	Susceptibility to JRA	[123]
Japanese	T	TNF-α –857	Susceptibility to RA	[74]
Japanese	C<T polymorphism	TNF-α –857	Association with severity	[124]
Thai	CA	TNF-α –863	Susceptibility to RA	[125]
Chinese	C<A polymorphism	TNF-α –863	No association	[47]
Taiwanese	C<A polymorphism	TNF-α –863	No association with severity	[72]
Turkish	CC	TNF-α –863	Susceptibility to JIA	[126]
Japanese	A	TNF-α –863	Susceptibility to JRA	[123]
Japanese	C<A polymorphism	TNF-α –863	Association with severity	[124]
Caucasian	A	TNF-α –863	Association with severity	[127]
Caucasian	C<A polymorphism	TNF-α –863	No association with JIA	[117]
Caucasian	C<A polymorphism	TNF-α –863	No association	[89]
Indian	A	TNF-α –863	Earlier onset in females	[6]
Japanese	T<C polymorphism	TNF-α –1031	Severity of RA	[124]
Japanese	C	TNF-α –1031	Susceptibility to JRA	[123]
Caucasian	T<C polymorphism	TNF-α –1031	No association with JIA	[117]
Caucasian	A	TNF-α +851	Susceptibility to JIA	[117]
Caucasian	A<G polymorphism	TNF-α +1304	No association with JIA	[117]
Dutch	Polymorphism	TNF-α +70	No association	[83]
Spanish	TNF-a6, b5	TNF-α microsatellite	Susceptibility to RA	[128]
Colombian	TNF-a6 allele, TNF-b4 allele	TNF-α microsatellite	Susceptibility to RA	[129]
Indian	TNF-b5 allele	TNF-α microsatellite	Susceptibility to RA	[130]

Table IV. Association of TNF-α polymorphism at various loci in etiopathogenesis of RA in various populations

JIA = juvenile idiopathic arthritis; JRA = juvenile rheumatoid arthritis; RA = rheumatoid arthritis; TNF = tumor necrosis factor

genotype as a genetic factor that contributes to radiologically detected erosions in RA patients. Considering the location of this polymorphism in a region involved in TNF-α gene transcription and its association with disease, they hypothesized that the –238G-to-A transition might influence TNF-α mRNA expression and, as a result, facilitate deregulation of the cytokine network, thereby influencing the disease process. In order to extend the association between the TNF –238 promoter polymorphism and the severity of RA, this group of investigators further reported that the TNF –238GG genotype contributes to the progression of joint destruction in RA, independent from HLA-DR4 [116]. Fabris et al. also suggested that TNF –238GG genotype associates with severity of RA, as TNF –238GA genotype was absent in severe but present in mild RA Italian patients [115].

Similarly, Rodríguez-Carreón et al. [24], studying Mexican RA patients versus healthy subjects, showed statistically significant difference in TNF-α –238GA genotype in two groups and reported that TNF-α –238A allele is a risk factor for RA in adulthood. Emonts et al. [89] also reported that the genotype TNF-α –238 G/A polymorphism was significantly associated with RA. These investigators concluded that the TNF-α –238 G/G genotype is overrepresented in RA patients when compared to controls (crude OR (95% CI) 2.48 (1.38-4.46) for TNF-α G/G vs. G/A). Since RA patients were significantly older than healthy controls and controls are by definition still "at risk" to develop RA at a later age, the difference observed may also result from a difference in susceptibility to develop RA at a younger age. Recently, Lee et al. [119] reported that the TNF-α promoter –238A/G polymorphism was not associated with susceptibility to juvenile idiopathic arthritis (JIA) in Europeans, while Jiménez-Morales et al. [90] reported that the TNF-α –238A allele has an association with JRA only in males and supported the concept that the TNF-α gene is a genetic risk factor for JRA in the pediatric Mexican population.

The causes for such variation in the published results from different populations are far from clear. The discrepancy of results has been attributed to the following reasons. First, genetic heterogeneity for JIA may exist in different populations. The prevalence of the A allele was found to vary among healthy controls of several ethnic groups from 4.1 to 26.9%. Its frequency was lowest among Mexicans and highest among Turks. Second, there are clinical heterogeneities or variations in sub-type of disease. Third, discrepancies may be caused by different linkage disequilibrium (LD) patterns, for example, these polymorphisms may be in LD with a nearby causal variant in one ethnic group but not in another [68,69,120].

TNF-α –376 polymorphism and susceptibility to RA

Only a few reports are available on the role of TNF-α–376 polymorphism and RA (Table IV), however the results are consistent showing no statistically significant association between TNF-α –376 polymorphism and RA in Chinese, Turkish, Caucasian, Spanish, and Taiwanese patients [47,62,72,89,117]. Emonts et al. [89] found significant difference in the frequency of GG genotype among the RA patients and controls ($p = 0.04$) however, on applying Bonferroni correction for multiple testing, the data were not significant. Further, the frequency of the TNF-α –376A alleles in the RA multiplex families was similar in several studies [116,131], indicating that these alleles occur too infrequently to play a major role in RA susceptibility in these populations.

TNF-α +489 polymorphism and susceptibility to RA

TNF +489 polymorphism, located in the first intron of the TNF-α gene was described in 1996 [113]. Van Krugten et al. [34] demonstrated that TNF +489A allele is associated with a decreased risk of developing RA independent of SE. A similar conclusion came from others, who reported that the +489

polymorphism is not in linkage with HLA class II alleles associated with RA [113,132]. These investigators suggested an independent contribution of TNF-α +489 polymorphism in RA susceptibility. In a retrospective analysis of consecutively selected RA patients from the Leiden, Netherland, Van Krugten et al. [34] showed a significant association of the +489GA genotype and less erosive disease in comparison to patients with the GG genotype. On the other hand, the association of the TNF +489G allele with a more severe course in RA (independent of DR4-homozygosity) was reported by Verweij et al. [133]. Mullighan et al. [132] reported an association of the TNF +489A allele with TNF production. Preliminary data on the functional relevance of the +489 polymorphism using allele-specific transcript quantification analysis suggested no transcriptional difference between the TNF +489A and TNF +489G allele. Thus the disease associations may have to be explained by linkage disequilibrium with alleles within or nearby the TNF/LT locus. Collectively, published data suggested that the TNF +489 polymorphism is part of a haplotype that is associated with less severe disease in RA and so probably associated with less TNF production in the joints of RA patients [115,117,122]. However, Low et al. [121] did not support the association of the TNF +489A allele with RA susceptibility or severity (Table IV).

TNF-α –857 polymorphisms and susceptibility to RA

It has been reported that allele –857T is associated with higher production of TNF-α, whereas allele –857C is associated with low TNF levels [134]. However, the results of the published data about the association of TNF-α –857 polymorphism with TNF expression are quite inconsistent [134-137]. Yen et al. [72] reported that the TNF-α promoter polymorphisms at positions 857 was not related to the clinical manifestations of RA in Taiwanese patients. Further, no significant association between RA patients and either genotype or allele frequencies of the TNF-α –857 polymorphism was detected in Chinese [47]. Although TNF-α –857A has been shown to influence RA susceptibility in individuals monozygous for the SE in Caucasian population [85], Emonts et al. [89] suggested that after correction for age (and gender), and multiple testing, TNF-α –857 polymorphisms were not associated with RA susceptibility or severity in Caucasians. The frequency of –857T allele was significantly higher in Japanese patients with systemic JRA [123]. These investigators concluded that –857T allele in combination with HLA-DRB1 0405 haplotype may be a systemic risk factor for JRA [123,134]. Overall, the analysis of published data (Table IV) from different ethnic groups showed lack of association between TNF-α –857 and RA in the majority of ethnic groups [47,68,72,89,117]. The results of these studies warrant for additional larger studies to elucidate the contributing factor of these polymorphisms in the susceptibility to, and severity of, RA.

TNF-α –863 polymorphisms and susceptibility to RA

TNF-α –863A polymorphism has been reported to be associated with RA susceptibility in Japanese [123,124], Turkish [126], and Thai populations [125]. The frequency of TNF –863A allele in Japanese patients with systemic JRA was significantly higher than those in controls. These results suggested that allele –863A might be a predisposing factor for systemic JRA, due in part to the higher promoter activity of the TNF-α gene [123], as individuals with allele –863A have been reported to produce higher levels of TNF-α [134]. It was also reported that –863A allele of the TNF-α –863 polymorphism is in strong linkage with HLA-B61 and DRB0901, which are known to contribute to RA susceptibility [134]. Recently Gambhir et al. [6] reported that allele A of TNF-α –863 polymorphism is associated with early onset of RA in Indian females. Udalova et al. [127] also found that –863A was predictive of severe erosive joint disease in HLA-DR4-positive individuals in UK population.

Contrary to these reports, Yen et al. [72] reported that the TNF-α –863 polymorphisms were not related to clinical manifestations of RA in Taiwanese patients. Further, no significant association between RA patients and either genotype or allele frequencies of TNF-α –863 polymorphism was detected in the Chinese [47]. Emonts et al. [89] suggested that after correction for age (and gender), and multiple testing, TNF-α –863 polymorphism was not associated with RA susceptibility or severity in Caucasians. These investigators suggested additional larger studies in order to elucidate the contributing factor of this polymorphism in the susceptibility to, and severity of, RA.

TNF-β +252 polymorphism and RA

In view of the highly critical role of TNF-α promoter polymorphisms in the pathogenesis of RA, it is important to examine the role of other members of the major histocompatibility complex (MHC) class III region in the pathogenesis of RA. TNF-β belonging to the surrounding of TNF-α locus has indeed been shown to play important role in the pathogenesis of several autoimmune diseases, including RA [138,139]. Immunological studies on TNF-β showed its close resemblance to TNF-α in terms of pro-inflammatory and apoptotic activity.

A polymorphism has been reported at position +252 within the first intron of the TNF-β gene, consisting of nucleotides guanine (TNF-β +252G) on one allele and adenine (TNF-β +252A) on the alternate allele [54]. The presence of G at this position defines the mutant allele known as TNF-β*1 (allele 1) which is less frequent allele and is associated with higher TNF-α and TNF-β production [54,140]. TNF-β A252G polymorphism (rs909253) affects a phorbol ester-responsive element. Association of TNF-β +A252G polymorphism has been reported with various autoimmune diseases including RA [48,141-143], Graves' disease [144], idiopathic membranous glomerulonephritis, IgA nephropathy [145], myasthenia gravis [146], asthma diathesis [147], SLE with nephritis [148], systemic sclerosis [149], and plaque psoriasis [150]. Recently, TNF-β +A252G polymorphism is also reported to be associated with both susceptibility to, and mortality from, sepsis [151,152].

Although there is a plethora of literature regarding the role of TNF-α polymorphism in the pathogenesis of a variety of autoimmune diseases, including RA, only few studies have been reported on the role of TNF-β in the pathogenesis of RA. The outcome of published data about the association of TNF-β +252 polymorphism with RA has been summarized in Table V.

Recently, we have reported the role of TNF-β +252 promoter polymorphism in Saudi RA patients, that GG genotype was susceptible to RA while GA was refractory [48]. Earlier, we found an associa-

Population/Group	Genotype/Allele	Suggested association with RA	Reference
Saudi	GG	Susceptibility	[48]
Tunisian	GG/G	Susceptibility	[60]
Belgian	A<G polymorphism	No association	[153]
Caucasian	GG	Susceptibility	[138]
Caucasian	A	Susceptibility	[143]
Caucasian	GG	Early age of onset	[143]
Japanese	A	Susceptibility	[141]
Swedish	A<G polymorphism	No association	[154]
Spanish	A<G polymorphism	No association	[79]

Table V. Association of TNF-β +252 polymorphism in etiopathogenesis of RA in various populations

tion of HLA-DRB1*04 and RA in Saudi patients. On the basis of these two studies, we concluded

that GG genotype of TNF-β together with HLA-DRB1*04 might contribute to the RA susceptibility. Our findings are similar to the observation made on Caucasian and Japanese populations showing that TNF-β +252 polymorphism together with HLA-DRB1*0405 influences the susceptibility to RA [141,143].

Panoulas et al. [138] from UK and Karray et al. [60] from Tunisia also reported that GG genotype of TNF-β +252 polymorphism occurs more frequently in RA patients as compared to general population. The GG genotype has been linked with higher levels of TNF-β (LT-α) [155], and therefore the presence of erosions in RA may be partially caused by higher levels of TNF-β in the affected joint. However, both TNF-α and TNF-β genes are located in the same area of the genome, and the two polymorphisms are in linkage disequilibrium. It is thus possible that association of the TNF-β +252 polymorphism with RA disease could be due to linkage with the TNF-α –308 polymorphism or to linkage of both polymorphisms with another disease marker located nearby, since there is a strong association between RA and certain HLA haplotypes, the genes of which are located along with the TNF locus in the MHC region, and there is evidence that genes closely associated with the MHC region are operative in RA. As these polymorphisms segregate independently (so called "genetic heterogeneity"), any one individual might respond to an insult with a pattern of cytokine expression quite different from the cytokine response another individual might mount. As *in vivo* cytokine interactions are complex, it is unlikely that a single allelic variant results in etiopathogenesis of RA. However, the collective influence of several factors could influence immune responses as complex as those underlying in RA and other autoimmune disorders. Published data supported an important role of ethnicity in the association of TNF-α and TNF-β polymorphisms and RA.

Anti-TNF-α therapy response and TNF-α genotypes

Anti-tumor necrosis factor (anti-TNF) therapies have revolutionized the treatment of RA [156,157]. Three drugs of this type, infliximab, etanercept, and adalimumab, have been used with success in hundreds of thousands patients with RA around the world. New drugs targeting TNF are in development or have been recently approved [158]. The beneficial effects of these drugs include a better quality of life, control of inflammation, stiffness and pain, and slowing progression to joint erosions and deformity. However, there is a significant percentage of patients who do not obtain these advantageous effects [156-158]. In some of these patients, this lack of response is primary, from the start of the treatment, whereas others develop resistance to treatment after a period of initial response. To workout useful predictors to forecast what the clinical response of a specific patient will be, multiple lines of research are being undertaken based on clinical features of patients (such as synovial tissue biomarkers, blood proteins) or genetic variants [159-162]. Very promising, though preliminary, findings have been reported in the field of genetics. Sixteen single-nucleotide polymorphisms (SNPs) with an important association with response to treatment were identified in a recent genome-wide association study [159]. However to date, the only replicated genetic predictor of anti-TNF response is the –308 G>A single-nucleotide polymorphism in the TNF-α promoter region (Table VI).

The presence of the TNF –308GG genotype appears to be a marker of good response to anti-TNF treatment. Good responders were defined, according to the European League Against Rheumatism (EULAR) consensus statement, as patients whose DAS28 score improved by at least 1.2 at week 22 compared with their DAS28 score before the first infusion [184]. Similarly, non-responders were defined as patients whose DAS28 score improved by < 1.2 [184]. Various reports using different anti-TNF-α blockers suggested that the presence of the –308GG genotype or G allele of TNA-α –308 polymorphism may help to define a subgroup of RA patients with a better response to this treatment [164,168,171-175]. A recent meta-analysis of previous studies confirmed that carriage of the allele-G at TNF –308 is

associated with a better response to anti-TNF treatment in comparison with patients homozygous for the allele-A among Caucasians [163].

The percentage of good responders was significantly higher in group GG than in group AA and AG of TNF-α –308 polymorphism. The most straightforward interpretation of these data is that in AA and AG patients, standard infliximab treatment is overwhelmed by the high production of TNF-α associated with –308AG or AA genotypes. It could be argued that poor outcome with infliximab only

Population/Group	Genotype/allele	Polymorphism	Response to anti-TNF-therapy	Reference
Meta-analysis	G allele	TNF-α –308	Better response	[163]
Review	A allele	TNF-α –308	Poorer response	[164]
Review	G<A	TNF-α –308	Better response	[165]
Review	A allele	TNF-α –308	Poorer response	[92]
Review	A allele	TNF-α –308	Poor response	[166]
Meta-analysis	G<A	TNF-α –308	No association	[167]
Meta-analysis	G<A	TNF-α –238	Better response to infliximab	[67]
Swiss	GG	TNF-α –308	Better response	[168]
Caucasian	AA	TNF-α –308	Poor response to etanercept	[160]
Caucasian	GA	TNF-α –238	Poor response to infliximab	[160]
Caucasian	G<A	TNF-α –308	No association	[169]
Caucasian	G<A	TNF-α –238	No association	[169]
Caucasian	G<A	TNF-α –308	No association	[170]
French	GG	TNF-α –308	Better response to infliximab	[171]
French	GG	TNF-α –308	Better responder to etanercept	[172]
Chilean	GA	TNF-α –308	Better response to infliximab	[173]
Chilean	GG	TNF-α –308	Better response to adalimumab	[174]
Chilean	GG	TNF-α –308	Better response to adalimumab	[175]
Swedish	GG	TNF-α –308	Better response to etanercept	[176]
German	G<A	TNF-α –308	Better response to etanercept	[177]
Serbian	GG	TNF-α –308	Better response to etanercept	[178]
Serbian	A allele	TNF-α –308	Poor response to etanercept	[64]
Spanish	G<A	TNF-α –308	No influence on infliximab	[179]
Spanish	G<A	TNF-α –238	No influence on infliximab	[179]
Spanish	G<A	TNF-α –308	No influence on prednisone	[180]
Portuguese	GG	TNF-α –308	Better response to infliximab	[65]
Portuguese	GG	TNF-α –308	Poor response to etanercept	[65]
Korean	GG	TNF-α –308	Better response to etanercept	[181]
Hungarian	GG	TNF-α –308	Better response to infliximab	[75]
Swedish	GG	TNF-α –308	Better responder to etanercept	[176]
Polish	G<A	TNF-α –209	No influence on leflunomide	[182]
Caucasian	SNPs	LTA-TNF	Better response to etanercept	[183]
Italian	GG	TNF-α –238	No association	[115]

Table VI. Association of TNF-α polymorphism with anti-TNF-α therapy response in RA

indicates that the AG or AA genotypes are associated with particular severity in RA patients. Contrary to these findings, some Authors did not observe any difference in disease severity between patients in group AA and AG (poor infliximab responders) and those in group GG (good infliximab responders) before treatment with infliximab [171].

Maxwell et al. [160] evaluated efficacy of anti-TNF treatment in Caucasian RA patients. They demonstrated a complex relationship between genotype at TNF-α –238 and –308 as well as treatment response that appears to differ according to the agent used. The RA patients carrying the rare TNF –308AA genotype responded poorly to etanercept, whereas genotype at this SNP did not associate with response to infliximab. Conversely, genotype at TNF –238 was associated with treatment response to infliximab, but not etanercept.

These findings were confirmed in a secondary analysis of the same patients, comparing the frequency of EULAR good and non-responders according to TNF –238 and –308 genotype. The association of the TNF –308AA genotype with response to etanercept, but not infliximab, raises important questions about the mechanistic differences between these two drugs, and the potential for genotype to differentially influence treatment response. Uniquely among the TNF antagonists, etanercept binds LT-α [185], and does so with similar affinity to soluble TNF [186]. Moreover, it has been demonstrated in inflammatory bowel disease that LT-α production can be influenced by genotype at TNF –308, with the AA genotype correlating with a high secretor phenotype [187]. It is possible, therefore, that in the presence of increased quantities of both TNF-α and LT-α in patients carrying the TNF –308AA genotype, the potency of etanercept is insufficient to neutralize both cytokines, with resulting poor treatment response. There are also profound pharmacokinetic differences between etanercept (a soluble receptor) and infliximab (a chimeric human-murine mAb), with infliximab having higher peak concentrations and bioavailability, and a significantly longer half-life. As a result, the ratio of area under the curve/time over the normal dosing period in RA is significantly higher for infliximab compared with etanercept [188], reinforcing the possibility of differential effects of genotype at TNF –308 polymorphism.

Very few reports are available on association between genotype at TNF –238 polymorphism and response to anti-TNF treatment in RA although genotype at this marker has been associated with X-ray damage in RA, and increased severity of disease [116]. In a cohort, TNF –238GA genotype was associated with a poorer response to infliximab. This was not seen in the etanercept-treated patients, in whom there was also no association between TNF –238 genotype and treatment response. It is possible, therefore, that the poorer response to infliximab relates to the chance event of this group having more severe disease (a known marker of poor treatment response) than the etanercept-treated patients of similar genotype. Fabris et al. [115] reported that the –238AG genotype is absent in severe-unresponsive RA, but present in mild-responsive RA Italian subjects and suggested that –238GG homozygosity associates with severity and unresponsiveness. Genetic variations in the TNF and HLA-DRBI region have also been reported to affect the response to treatment of early RA [183]. Genotyping RA patients early in their disease course may help identify those with a poor prognosis and thus lead to a more aggressive treatment of their disease.

Future directions for research

Future studies should be undertaken using significantly larger samples of RA patients from various ethnic groups including non-Caucasians. The population should be stratified according to ethnicity, age, and gender. The diagnosis and severity of the disease should be based on uniform diagnostic criteria precisely describing the characteristic of individual with regards to symptoms, pattern, and functionality. Future studies should clearly identify the potential risk factors of the disease. Such information will ultimately support the research for developing novel and effective preventive measures, and establishing efficacious treatment/management strategies for RA.

The review in brief	
Clinical question	Tumor necrosis factor (TNF)-α and -β have been shown to play a pivotal role in the pathogenesis of RA. The present review analyzes the role of TNF-α and TNF-β gene polymorphism in the pathogenesis of RA
Type of review	Narrative
Search of the literature	Medline search using the following keywords: Tumor necrosis factor, TNF-α, TNF-β, Rheumatoid arthritis, Polymorphism, Drug response to RA
Conclusions	The present review concludes that: • The alleles and genotypes of TNF-α and TNF-β polymorphisms are significantly associated with susceptibility to, and severity of, RA • The genetic variants of TNF-α and TNF-β polymorphisms provide a rationale to identify the population at risk of developing RA • Genotyping of TNF-α and TNF-β genes may be a useful tool for predicting response to the treatment • An important role of ethnicity in the association of TNF-α and TNF-β polymorphisms and RA has been suggested • In-depth genetic studies using larger sample from various ethnic groups are warranted
Limitations	Review of the literature showed significant discrepancies in results, which may be attributed to small sample size in most of the studies, improper stratification of RA patients, and significant variations in methods of diagnosis. The number of investigated patients has to be increased to establish the possibility of subdivision of the cohorts according their clinical symptoms, severity of disease, HLA status, and also with respect to individual genetic factors

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