Association of Cytokine Gene Polymorphism with Susceptibility of Ankylosing Spondylitis

Raisa Enayet Badhan[1], *Shaheda Anwar[2], Ahmed Abu Saleh[2], Shaila Akhtar[3], Taskin Jahan[4], Md. Jahangir Alam[5]

[1] Medical officer (Microbiology), Sheikh Hasina National Institute of Burn and Plastic Surgery, Dhaka, Bangladesh.

[2] Department of Microbiology and Immunology, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

[3] Lecturer, Department of Microbiology, Green Life Medical College, Dhaka, Bangladesh.

[4] Lecturer (Department of Microbiology), Chattagram International Medical College and Hospital, Chattagram, Bangladesh

[5] Resident (Department of Ophthalmology), Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

***Corresponding Author**

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ABSTRACT

This article reviews various studies on cytokine polymorphism in ankylosing spondylitis and looks for the associations between the susceptibility to disease. To find the pertinent research, a thorough search of the literature was undertaken. Articles were chosen for this review should be met some criteria: Studies should be case control studies, should described the association between the cytokine gene polymorphism (IL-1R2, IL-12B, IL-10, TNF-α and IL-23R) with the pathogenesis of AS, frequencies of genotypes and alleles in case and control groups could be collected. This article reviewed 20 different studies on Cytokine gene polymorphisms. Nine single-nucleotide polymorphisms (SNPs) of IL-23R (rs11209026, rs1004819, rs10489629, rs11465804, rs1343151, rs11209032, rs1495965, rs7517847, rs2201841) are linked to AS susceptibility out of the seventeen SNPs. Additionally, based on ethnicity revealed a noteworthy association between seven IL-23R SNPs and AS susceptibility in Americans and Europeans, but not in Asian population. Furthermore, susceptibility to AS is also conferred by the IL-10–819 C/T, IL-10-1082A/G, G/G genotype and TNF-α−857 C/T polymorphisms, particularly in Asian populations. IL- 1R2 in rs 2310173 polymorphism found to be associated with AS in European, not in Asian.

Keywords: Single nucleotide polymorphism, Interleukin, Tumour necrosis factor, Ankylosing spondylitis.

INTRODUCTION

The chronic inflammatory condition known as ankylosing spondylitis (AS) is characterized by the destruction of cartilage and bone, peripheral arthritis, and axial skeletal ankylosis [1]. This disease primarily affects individuals between the ages of 20 and 60, and its high occurrence results in a significant

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socioeconomic burden [2]. While the precise immunopathogenesis of this illness remains unclear, a number of studies have suggested that several susceptibility loci contribute significantly to AS vulnerability. More and more data has been suggested that other genetic loci, such as IL-1R2, IL-12B, IL-10, TNF- α, and IL-23R, may also play a role in the aetiology of AS.

Based on genome-wide association studies, IL-23, an IL-12-related cytokine, is thought to be a possible non-HLA candidate in autoimmune illness (GWAS) [3]. Through its ability to promote Th17 cell differentiation and proliferation, IL-23 may have a role in the development of AS [4]. A number of single-nucleotide polymorphisms (SNPs) of the IL-23R have been substantially linked to AS in a number of recent studies, while other research has shown conflicting findings [5-8]. Regarding IL-12B, this gene is 15 kb long, has eight exons, and is mostly controlled at the post-transcriptional level. It is situated in the non-HLA region of chromosome 5q31–33[9]. The relationship between IL-12B polymorphism and the likelihood of developing autoimmune illnesses has been the subject of numerous studies [10-12], but the findings have generated debate [13]. The IL-10 gene is found on chromosome 1 at 1q31–q32[14]. Several SNPs, including −1082G/A, −819 C/T, and −592C/A, have been identified within this area [15]. According to earlier research, IL-10 levels were considerably greater in AS patients than in healthy controls, suggesting that this cytokine may be crucial in the onset of AS [16]. TNF-α is a further contender, exhibiting multiple polymorphism sites within the promoter, including −308 (G/A), −238 (G/A), and −857 (C/T) [17-19]. While some research have hypothesized that these allelic variations would be functionally meaningful [20,21], other publications have shown no discernible changes in the distribution of alleles [22-23] Furthermore, the substantial association between the development of AS and IL-1R2 rs2310173 was first shown by a recent GWAS in a sizable European people [24]. These findings provide evidence for a potential correlation between the pathophysiology of AS and the cytokine gene polymorphisms, such as IL-1R2, IL-12B, TNF-a308A/G, TNF-a-238 A/G, TNF-a-857 C/T, IL-10–819 C/T, IL-10–592 C/A, IL-23R rs11209026, rs1004819, rs10489629, rs11465804, rs1343151, rs10889677, rs11209032, rs1495965, rs7517847, and rs2201841. The relationship between the gene polymorphisms and the disease susceptibility can be summarized in the review article.

METHODOLOGY

Articles to be reviewed were chosen from PubMed, Elsevier Science Direct, China National Knowledge Infrastructure database, Chinese Biomedical database, and Google Scholar. We have chosen the studies for this review should be met the following criteria: (1) Studies should be case control studies. (2) Studies should described the association between the cytokine gene polymorphism (IL-1R2, IL-12B, IL-10, TNF-α and IL-23R) with the pathogenesis of AS; (3) The frequencies of geno types and alleles in case and control groups could be collected. Studies included at this review are shown in Table 1.

Table 1: Characteristics of individual studies included in the review article

Cytokine gene	First author	Year	Ethnicity	Study population (cases/controls)	Gene polymorphism
IL-1 α/IL-Ra	Tekaya*et al* [33]	2020	Africa	100/100	-889C/T
IL-1R2	Bang *et al* [30]	2011	Asian	1164/752	rs2310173
	Chen [31]	2012	Asian	200/200	rs2310173
	Xia *et al* [32]	2015	Asian	490/580	rs2310173
IL-12B	Wong *et al* [15]	2012	Asian	362/362	rs3212227

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	Zhou [12]	2013	Asian	297/370	rs3212227
IL-10	Lee *et al* [38]	2009	Asian	142/166 106/141	-819 C/T; -592C/A -819 C/T; -592C/A
	Lv *et al* [39]	2011	Asian	110/120	-819 C/T; -592C/A
	Braga *et al* [37]	2021	American	149/169	-1082G/A
TNF- α	Chung *et al* [20]	2011	Asian	119/135	238G/A; 308G/A; 857 C/T
	Tong *et al* [41]	2012	Asian	106/106	238G/A; 308G/A; 857 C/T
	Ji *et al* [42]	2013	Asian	57/30	238G/A; 308G/A; 857 C/T
	Manolova *et al* [43]	2014	European	58/177	308G/A
	Cai [25]	2009	Asian	112/96	857 C/T
IL-23R	Sung *et al* [8]	2009	Asian	451/392	rs11209026; rs1004819; rs10489629; rs11456804; rs1343151; rs10889677; rs11209032; rs1495965; rs7517487; rs2201841
	Wong *et al* [15]	2012	Asian	362/362	rs10889677
	Dong *et al* [44]	2013	Asian	291/312	rs11209032; rs7517847
	Daryabor *et al* [45]	2014	European	294/352	rs1004819; rs11209032; rs1495965
	Su *et al* [46]	2016	Asian	157/150	rs1004819; rs10489629; rs1343151; rs10889677; rs11209032; rs1495965
IL-17A, IL-17F	Wielinska *et al* [47]	2021	European	138/190	rs2275913, rs763780, rs4819554, rs708567

FINDINGS OF DIFFERENT STUDIES

Chronic inflammation is linked to axial and peripheral skeleton abnormalities in AS, an autoimmune rheumatic illness [14]. There has reportedly been an increase in studies over the past few years that examine the part that genetic predisposition plays in AS [5-8], [25-29]. Some of the findings, meanwhile, were debatable. There could be a number of explanations for the contradicting findings, including true genetic variation, ethnic differences, and small sample sizes. This review is carried out to provide a more concise summary of the relationship between the aforementioned gene polymorphisms and the onset of AS.

Particularly, human monocytes, neutrophils, and B cells express the IL-1R2 gene. IL-1R2 is a member of the IL-1 family, which plays a crucial role in the etiology of numerous inflammatory and autoimmune disorders.

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IL-1/ IL-1R

The IL-1R2 polymorphism rs2310173 was not linked to AS in the Asian population according to this review. In contrast, it was found that in patients from Europe, this SNP was strongly linked to AS [30-32]. Another study shows, polymorphisms of IL-1/IL-1Ra cytokines seem to be involved in susceptibility and clinical course of SpA in Tunisian patients [33].

IL-12B

The 15 kb long, eight exon-rich IL-12B gene is found on chromosome 5q31–33, outside of the HLA area. Its expression is primarily controlled post-transcriptionally [34].

Many SNPs in the IL-12B gene have been studied in AS patients, however the findings have generated debate [15, 35].

IL-10

According to earlier research, patients with AS appear to produce considerably more IL-10 from CD8 cells than do healthy controls [16]. Numerous cytokines, including IL-10, have known hereditary predispositions [36, 37].

We thus looked at the IL-10 polymorphisms in AS. Our findings demonstrated a substantial difference in the distribution of IL-10–819 C/T allelic frequencies between the AS patients and the control group. On the other hand, there was no discernible link found between AS and IL-10–592C/A allelic polymorphisms. These results concur with those obtained by Lee et al. and Lv *et al.* [38, 39]. Braga *et al.* found association of IL- 10-1082 A/G and G/G genotype with susceptibility to AS in Asian population [40].

TNF- α

In this investigation, we discovered a correlation in allelic contrast between TNF-α−857 C/T and AS in every study participant. Nevertheless, neither the total population nor any subgroups showed any discernible correlation between AS susceptibility and TNF-α−238 polymorphisms. Regarding TNF-α−308, allelic comparisons showed no connection across all participants; however, when Asian and American populations were stratified by ethnicity, an association was seen. This finding contradicted a prior study that demonstrated that allele A at position 308 had a population-wide protective effect against AS [20,25, 41-43].

IL-23R

A number of immune cells, including memory T cells, effector T cells, natural killer cells, dendritic cells, and macrophages, bind to the receptor for the inflammatory cytokine IL-23[4]. Numerous autoimmune disorders have been studied in relation to IL-23R, and susceptibility alleles for the protein have been linked to psoriasis arthritis, Crohn's disease, and inflammatory bowel disease [5, 8, 28].

Except for rs10889677, our results indicate a strong correlation between the IL-23R polymorphisms and AS susceptibility in the general population. It is commonly recognized that because geographic factors induce population dispersion and, in turn, genetic diversity, allelic frequencies of genes frequently differ significantly among various geographic populations.

Seven SNPs of IL-23R, for instance (rs11209026, rs1004819, rs10489629, rs11465804, rs1343151, rs11209032, rs1495965) have been shown in our study to be strongly associated with AS in both Europeans and Americans; however, there is no significant difference between these IL-23R SNPs in the Asian population [8, 15, 44-46].

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IL-17A, IL-17F

Another study showed the association of IL-17 F rs 763780 and IL-17 RA rs48419554 G allele with disease severity and can be a potential biomarker of disease severity [47].

Large-scale studies involving many ethnicities should be taken into consideration in the future to confirm genetic correlations with AS susceptibility.

CONCLUSION

In conclusion, this review indicates that the IL-23R polymorphisms, with the exception of the rs10889677, are associated with AS susceptibility. In the subgroup analysis, significant associations were shown in European and American population, but not in the Asian population. This review also found that IL-10–819 C/T, IL- 10-1082 A/G and G/G genotype and TNF-α−857 C/T polymorphism might be associated with AS risk, especially in the Asian population. With the exception of rs10889677, the results of this review suggest that the IL-23R polymorphisms are linked to AS susceptibility. Significant connections were found in the subgroup analysis for the American and European populations, but not for the Asian population. Additionally, our findings suggested that TNF-α−857 C/T polymorphism and IL-10–819 C/T, IL-10-1082 A/G, G/G polymorphism may be linked to AS risk, particularly in the Asian population.

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