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A General Sight about Linking PARP-1 and NFKB1 Variations to the Inflammatory Events

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Abstract

Poly (ADP-ribose) polymerase-1 (PARP-1) has various roles in cellular processes such as DNA repair, genomic stability, transcription, stress response, and cell death via regulating death and inflammation signalling pathways. On the other hand, PARP-1 inhibition has been shown to provide benefits in experimental models of animals with inflammatory diseases such as asthma, atherosclerosis and diabetes. PARP-1 also acts a transcriptional coactivator of nuclear factor kappa B (NFKB). The NFKB is a ubiquitous transcription factor that controls the expression of genes encoding cell adhesion molecules, growth factors, cytokines, and some acute phase proteins. Inappropriate activation of NFKB has been mostly searched with inflammatory events. In complete and persistent inhibition studies of NFKB, apoptosis, inappropriate immune cell development and delayed cell growth were investigated. These findings might provide new perceptions in the pathogenesis of inflammatory disorders regarding the roles of PARP-1 and NFKB1 proteins. In this review, we focus on some variations (rs28362491, rs696, rs1136410, rs2793378, rs7527192) of PARP-1 and NFKB1 genes in relation to susceptibility to common inflammatory diseases including rheumatoid arthritis, systemic lupus erythematosus, allergic rhinitis, Graves' disease, Hashimoto's thyroiditis, asthma and Behcet's disease.

Keywords: Inflammatory diseases; Nuclear factor-kappa B; Poly (ADP-Ribose) polymerase-1; Polymorphism

Abbreviations

SNP: Single Nucleotide Polymorphism; PARP-1: Poly (ADP-Ribose) Polymerase-1; NFKB: Nuclear Factor-Kappa B; AR: Allergic Rhinitis; HT: Hashimoto's Thyroiditis; RA: Rheumatoid Arthritis; GD: Graves' Disease; T2DM: Type 2 Diabetes Mellitus; CD: Crohn's Disease; IL-1β: Interleukin-1β; IL-6: Interleukin-6; TNF-α: Tumor Necrosis Factor-A; GWAS: Genome-Wide Association Studies

Introduction

Inflammation is a significant factor in the pathogenesis in many disorders, especially autoimmune ones. As it is known that, autoimmune diseases develop when the body's immune system attacks its own healthy tissues, leading to prolonged inflammation, which may go along with the chronic inflammatory situations are defined by long-term inflammatory processes as a result of apoptosis [1,2]. Excessive activation or inappropriate regulation of immune cascades causes tissue and cellular damage which then leads to dysfunction and cell death via DNA damage. Affected cell, in autoimmune diseases, is damaged by initiating a programmed cell death via massive DNA damage. It is clearly demonstrated that, there is an important enzyme causing massive DNA damage in inflammatory situations called poly (ADP-ribose) polymerase-1 (PARP-1) [3]. **PARP-1 has been included in inflammatory response by regulating expression of inflammation-related genes like interleukin 1 (IL-1) [4]. Hassa and Hottiger** stated that PARP-1 also acts as a coactivator of celebrated ubiquitous transcription factor called nuclear factor-kappa B (NFKB). In other words, PARP-1 is required for specific NFKB-dependent gene expression in vivo [5,6]. On the other side, inflammatory processes are related to the enhanced gene expression of the immune mediators. *Transcription factors* are essential for the *regulation* of *gene expression.* NFKB, one of the most famous transcription factor, is an important mediator in the regulation of various biologic processes such as innate and adaptive immune responses, acute phase reaction, and apoptosis [7]. The function of NFKB is inhibited by binding to the NFKB inhibitor protein (IkB). Abnormalities in the NFKB regulation are concluded in multiple human pathologies which are inflammatory diseases, immune deficiencies and tumors. As PARP-1 and NFKB are responsible for the regulation of many inflammatory gene expressions in disease progression, variants in the genes coding for the NFKB and PARP-1 proteins could be potentially involved in the pathogenesis of the inflammatory and autoimmune disorders.

Recently, 653 SNPs have been reported in NFKB1 gene, accessed November 6th, 2014), and the functional -94 ins/del ATTG polymorphism (rs28362491) is the most frequently studied among them which causes insertion/deletion of ATTG at 94 site of the promoter region in NFKB1 [8]. Moreover, there is another polymorphism that is frequently studied with NFKB1 polymorphisms, named as 3' UTR A→G polymorphism (rs696) of NFKBIA gene (the inhibitor gene of NFKB1). Goto et al. showed that the alterations of the expression of IKBα protein which is encoded by NFKBIA was related with rs696 on NFKBIA and resulted in a change in NFKB activity [9].

2465 SNPs have been reported in PARP-1 gene until today, Among all polymorphisms in PARP-1 gene, one of the most studied variants is Val762Ala polymorphism (T2444C) (rs1136410) which is a missense variant. rs1136410 results in the substitution of alanine (Ala) for valine (Val) at codon 762 in the catalytic domain has been searching in susceptibility to many inflammatory situations for years [10-12]. The

polymorphisms of the promoter region (-410 C/T (rs2793378) and -1672 G/A (rs7527192)) in PARP-1 gene have been also investigating in the inflammatory situations [13,14].

We determined that, analyzing the studies about both of them may be a senseful and beneficial way to understand the interactions of these two genes in **inflammatory and autoimmune disorders.** In this brief review, we have summarized several supporting lines of evidence that PARP-1, NFKB1 and NFKBIA gene variants might have roles for pathogenesis of several related inflammatory and autoimmune diseases.

PARP-1

Poly (ADP-ribose) polymerase-1 (PARP-1) is the most celebrated and well–characterized member of the PARP family [15]. PARP-1 is involved in various cellular processes such as gene expression, amplification, malignant transformation, differentiation, division, DNA replication, mitochondrial function, DNA repair, chromatin replication, transcriptional regulation, cell death, and inflammatory response [16,17]. The human PARP-1 gene includes 23 exons spanning 43 kb and is located in 1q41–q43. The PARP-1 enzyme is a 116-kDa protein and contains three main domains: an N-terminal, DNA-binding domain (42 kDa) that contains a nuclear localization signal (NLS); a central automodification domain (16 kDa); and a C-terminal, catalytic domain (55 kDa). PARP-1 also enables various inflammatory responses by inducing inflammation-relevant gene expression such as adhesion molecules, oxidation-reduction-related enzymes, and cytokines [15,18-20].

In DNA-damaged cell, the damage is recognized by PARP-1 in a short time which in turn, affects many proteins to form a structure, and acts as a transcriptional coactivator of NFKB in cell nucleus [6,21-23]. PARP-1 uses NAD+ to form (ADP-ribose) polymers on target proteins [24]. NFKB1 and PARP-1 genes are frequently considered as a key point of crosstalk about inflammatory disorders [5,25,26].

NF-kappaB

NFKB is a widespread transcription factor which dominates the gene expression of some acute phase proteins, cytokines, growth factors, chemokines and cell adhesion molecules in every mammalian cell [27,28]. Also in many cell types, NFKB plays a key role in numerous processes physiologically and pathologically such as immune response, cell adhesion, differentiation, proliferation, angiogenesis, and apoptosis [29]. Moreover, NFKB is induced by intra- and extra-cellular stimuli including several agents such as cytokines, oxidant free radicals, inhaled particles, ultraviolet irradiation, and bacterial or viral products [30-32]. In non-stimulated cells, NFKB proteins form homo- or heterodimers that are sequestered in cytoplasm interacting with IkB inhibitors [33].

Five NFKB family members contain NFKB1 (p50/p105), NFKB2 (p52/p100), p65 (RelA), RelB, and c-Rel in mammals [34]. NFKB1 gene is localized to 4q23-q24 and consists of 24 exons, spanning 156kb. This gene encodes two proteins; a non-DNA binding cytoplasmic molecule p105 and a DNA binding protein p50. NFKB1 (p50)/ReIA (p65) hetorodimer is the common NFKB/Rel complex. The IkBα, an inhibitory version of NFKB1 protein, is regulated by NFKB1 and coded by NFKBIA gene. This gene, located at locus 4q13, contains 6 exons spanning 3.5 kb. NFKBIA gene is composed of three regions: N-terminal region with phosphorylation sites to regulate signal dependent degredation of IkBα through the ubiquitin-proteasome pathway, ankyrin repeat domain physically associated with NFKB proteins and C-terminal PEST region, regulating basal degredation [35-37].

NFKB-dependent gene activation is strongly modulated by PARP-1 as mentioned previous section. PARP-1directly binds to both p65 and p50 subunits of NFKB functioning like an adapter molecule, and connects NFKB to the basal transcription machinery so its inhibition diminishes proinflammatory cytokine response by decreasing transcription activation complex formation [5]. However, this function does not depend on DNA binding and enzymatic activity of PARP-1 [38].

The role of NFKB1 and PARP-1 inflammatory disease

The basic role of NFKB is, managing the expression of multiple immune and inflammatory genes involved in inflammatory diseases by their abnormalities. Inappropriate NFKB activation is associated with many human diseases and pathologic conditions such as UC [39], SLE [40], asthma [41], RA [42], septic shock [43], diabetes [44], cancer [45], AIDS [46], and atherosclerosis [47]. High levels of NFKB activation are found in IBD such as UC and CD [48,49], Furthermore, inappropriate NFKB activation in IBD, resulting in colonic tissue damage, is mainly due to pro- and anti-inflammatory cytokines such as IL-1, IL-6, IL-8, IL-12 and TNF-α [50]. According to a study, the absence of PARP-1 in a mouse model of Salmonella-induced inflammation due to decreasing NFKB–mediated proinflammatory gene expression, was associated with delayed gut inflammation, [51]. In addition, NFKB signaling acts as an initiator in tumour development by increasing tumour angiogenesis and proliferation, anti-apoptotic mechanism and immune response repression [52].

There is a growing amount of evidence that variations within the NFKB1 and NFKBIA genes potentially influence the function of NFKB during development of common inflammatory and autoimmune diseases both in health and various disease conditions such as ulcerative colitis [8,53], Crohn's disease [54], RA, SLE [55], psoriatic arthritis [56], giant cell arteritis [57], Celiac disease [58], Type 1 diabetes [59], oral submucous fibrosis [60], and oral squamous cell carcinoma [60].

It has reported that PARP-1 mostly plays a key role in cell death following numerous inflammation situations such as ischemia reperfusion damage [61], haemorrhagic shock, septic shock [62], lung inflammation [63], diabetes mellitus [64], autoimmune nephritis [65], chronic inflammatory disorders such as arthritis and IBD [66], and diseases of the central nervous system [67]. PARP-1-deficient mice showed decreased PARP-1 expression, a significant parameter in the endothelial dysfunction pathogenesis of diabetes [64], regulates the progression of autoimmune nephritis [65]. PARP-1 controls the expression of proinflammatory genes and/or inducing cell death in the injured tissues [68]. It has been stated that PARP-1 has a central role in various diseases as up-regulated PARP-1 expression co-localizes with DNA breaks and correlates with sepsis-induced inflammation and early and late stages of myocardial dysfunction in a septic rat model [69]. In summary, the studies presented in this section highlight the imbalance of NFKB and PARP-1 which has been involved in various diseases. However, which specific polymorphisms in these genes are associate with the mechanisms of disease development are unclear.

NFKB1 and PARP-1 polymorphisms in relation to inflammatory diseases

Rheumatoid arthritis and systemic lupus erythematosus

RA and SLE are complex diseases characterized by chronic inflammation with contributions of systemic autoimmunity [10,70]. The PARP-1 and NFKB1 genes may be the suitable candidate genes for investigating autoimmune and inflammatory disorders such as RA and SLE as genetic aspect.

Our previously published data suggest, rs1136410, the polymorphic marker localized to the coding region of the PARP-1 gene, is not related to development of RA in Turkish population [10] (Tables 1 and 2). In other clinical study, AA (mutant) genotype in rs1136410 has shown to be related with arthritis in 350 Korean SLE patients and 330 healthy controls [71]. Ala allele of rs1136410, leading to decreased enzymatic activity of PARP-1, was described [19]. In addition, according to the study which included 213 Spanish RA patients and 242 healthy subjects as controls, CA microsatellite repeat and rs2793378, C1362T variants in the promoter region of the PARP-1 gene, found to be a risk factor for susceptibility to RA in the Spanish population [14].

Many researchers have also pointed that variations within the NFKB1 gene could potentially influence the function of NFKB protein and in turn the process of inflammation. Recently, it has been shown that NFKB has been activated in rheumatoid arthritis synovium and resembled in inflammation mediators from RA, suggesting a role in the control of inflammation [72]. According to Simmonds et al. the inhibition of the NFKB pathway is believed to have a potential as a therapeutic target in RA [42].

Wong et al. showed that, the activation of NFKB is decreased in SLE patients but not in RA patients [40]. According to Orozco et al. NFKB1 SNP rs28362491 did not play a role in the development of RA and SLE in Spain population including 272 RA patients, 181 SLE patients, and 264 healthy individuals [55]. However, homozygosity of del allele of rs28362491 has an increased risk of RA in Spain population [73]. Besides, del/ins genotype was found as a decreasing risk for SLE in 224 SLE patients and 256 control subjects Chinese population [70].

Hashimoto's thyroiditis

Hashimoto's Thyroiditis (HT) is a chronic inflammatory and autoimmune disease of thyroid gland affected by interaction of multiple genes and various cytokines. Human leukocyte antigen (HLA) and immune regulatory genes (i.e., CTLA-4 and others) have been studied as possible risk factors for HT for years [74]. PARP-1 gene becomes a candidate gene for searching immunity as well as HLA and CTLA-4.

As Wang et al. determined, PARP-1 SNP rs1136410 reduces the enzymatic activity of enzyme about 40%, so SNP rs1136410 becomes a considerable variant for understanding the relationship between this gene and inflammatory diseases [19]. In our study, enrolled with 141 HT patients and 150 controls in a group of women in Turkish population, heterozygous genotype (Val/Ala) and Ala allele of rs1136410 and heterozygous (GA) and A allele of rs7527192 were found to be as protective factors against HT [75] (Tables 1 and 2).

On the other hand, we also previously investigated the susceptibility of rs28362491 and rs696 in NFKB1 and NFKBIA genes in HT disease because of the significance of NFKB1 as an immune-related gene. There was no considerable differences in the frequency of genotypes and alleles of these two variants in single However, combining multiple variants resulted in greater predictive power of disease risk. As we analyzed the combined effects of NFKB1 and NFKBIA polymorphisms in 120 HT patients and 190 controls in Turkish population, we found that ins/ins/AG combined genotype had a protective role and this protectiveness was based on G allele of rs696. On the other hand, increasing IL-6 serum levels were accompanied with deletion of rs28362491 in NFKB1 [76] (Tables 1 and 2).

Asthma

Asthma is a common and heterogeneous respiratory disease featured by lasting airway inflammation with bronchial hyper-responsiveness increase and reversible airway obstruction. Epidemiological and twin studies have shown that genetic and environmental factors are both responsible for this disease [77]. It has been suggested that numerous genetic factors are related to the susceptibility for asthma. PARP-1 experiments and therapeutic studies with PARP-1 inhibitors have indicated that an increasing inflammation in various situations such as asthma, pointing PARP-1 as a candidate gene. The protective effect of PARP-1 against asthma development may be related with its decreased enzymatic activity due to Ala 762 variant of Val762Ala polymorphism. It may affect expression of genes involved in inflammatory response. Our findings suggested that, Val allele had 5 times risk for developing asthma in comparison to the patients without the allele. We also found that PARP-1 762 Val/Ala and Ala/Ala genotypes had decreasing risk ability of adult asthma with respect to their wild-type homozygotes by univariate regression analysis model. Therefore, in a Turkish population of 180 controls and 112 patients with asthma, we provide evidence that, an amino acid substitution in a variant of PARP-1 gene had a protective role for asthma [77] (Tables 1 and 2).

Inflammatory airway diseases in humans have been associated with adhesion molecule expression and cytokine, correlating with the activation of NFKB in bronchial biopsies from asthma patients. Park et al. found that, rs2233407 A→T promoter polymorphism in NFKBIA gene was associated with development of atopic asthma by regulation of gene expression at the transcriptional level in 598 asthma patients and 183 controls in a Korean population [78].

Allergic rhinitis

Another chronic inflammatory disease is allergic rhinitis (AR) characterized by mucosal inflammation. The pathogenesis of AR and other allergic diseases are developed by the exposure to irritating complex substances and in response to respiratory allergens [79].

PARP-1 is the probable candidate gene as therapeutic approaches using PARP-1 inhibitors, indicates an improvement of systemic or tissue inflammation. We did not find any differences in allele or genotype frequencies of PARP-1 C410T (rs2793378) and Val762Ala (rs1136410) polymorphisms. However, heterozygote genotype of the promoter polymorphism G1672A (rs 7527192) was significantly found to be associated with the susceptibility to 110 AR patients compared with 130 controls. In haplotype analysis, PARP-1 C410T, G1672A and Val762Ala polymorphisms were not associated with an increased risk for AR. These results proved that the promoter G1672A polymorphism of the PARP-1 gene may be a risk factor for AR in Turkish population [79] (Tables 1 and 2).

Graves' disease

Graves' Disease (GD) is an organ specific autoimmune thyroid disorder characterized by diffuse goiter, hyperthyroidism, dermopathy, and an ocular disorder. GD is an autoimmune disorder. Hence it may be affected by a co-operation of multiple genes such as NFKB1, NFKBIA, PARP-1 and cytokines like IL-1β, IL-6, and TNF-α. It has been found as high as 79% contribution of genetic factors in GD development. We suggest that, PARP-1 and NFKB1 gene polymorphisms may be risk factors for developing GD and ophthalmopathy [80].

We found that, by means of rs7527192, patients with GG genotype and carriers of G allele were in a risk group of having GD. Patients with GG genotype and G allele have an increased risk of having the disease by 2.4 and 1.5 fold, respectively. We did not find any significant relationships or differences in patient and control groups for rs2793378, but found that rs2793378 was associated with ophtalmopathy as having C allele may be a risk factor for developing ophthalmopathy in GD patients.

In addition to this finding, when we genotyped the GD patients from the point of rs28362491, it has been noticed that del/ins genotype was a risk factor for GD in 120 cases and 150 controls in a Turkish population. The del/ins genotype of rs28362491 may also be related to the development of ophthalmopathy. We concluded that having ins/ins genotype may have a protective effect on the disease. There was no differences regarding rs696 in this study [80] (Tables 1 and 2). Therefore, our data on PARP-1 and NFKB1 polymorphisms may have added new pieces into the puzzle of underlying mechanisms of GD; however our suggestion requires replication by other case control studies before definitely establishing such a link.

Behçet's disease

Behçet's disease (BD) is a systemic autoimmune and chronic inflammatory disease characterized by recurrent oral ulcers, skin lesions, genital ulcers, vasculitis and ocular inflammation [81]. The exact cause of BD is still unknown, but there are some evidences that both, genetic and environmental factors are involved. NFKB1 and its inhibitor NFKBIA are important factors mainly involved in the inflammatory cascade of BD. One of the most prominent polymorphisms identified within the promoter of NFKB1 gene is -94 ins/delATTG m (rs28362491). The polymorphisms in the promoter regions of NFKB1 may result in altered NFKB1 expression,which in turn results in altered transcription of the inflammatory cytokines and may explain the overexpression of these cytokines and increased serum concentrations in BD. In our study, rs28362491 promoter variation has been analyzed in 89 BD and 190 healthy controls in a Turkish population. We found that the patients with ins/ins genotype and ins allele of 28362491 promoter have an increased risk of having the disease by 2.5 and 1.8 fold, respectively [82] (Tables 1 and 2). On the other hand, NF-kB is inhibited by binding to inhibitor (IKBα) and imbalance of NF-kB and IKBα have been involved in many inflammatory diseases. Recently, Hung et al. investigating NFKB1A promoter polymorphisms such as -881A/G,-826 C/T,-550A/T,-519C/T demonstrated that -826 T/T genotype is associated with skin lesions in patients with BD [83]. In addition to all these studies, we reported that the AA genotype of 3 UTR A>G polymorphism (rs696) in NFKBIA gene was significantly higher in BD patients. AA genotype had a 2.5 times risk factor for development of BD [82]. We have been also reported rs28362491 and rs696 variants' combined effects in BD disease. Combining multiple variants may result in greater predictive power of disease risk. Song et al. have stated that combined genotype of ins/ins+del/ins and GG was associated with the risk of sporadic cancer and as shown in previously published research, ins/ins+AG combined genotype and also ins allele frequencies were higher in BD patients considerably [84].

Studies	Controls n (%)				Patients n (%)			p
	WW	WD	DD		WW	WD	DD	
Rheumatoid Artrit								
rs1136410	60 (36.4)	88 (53.3)	17 (10.3)		62 (48.4)	51 (39.8)	15 (11.7)	>0.05
Hashimoto's Thyroiditis								
rs1136410	77 (51)	61 (41)	12 (8)		98 (70)	31 (21)	12 (9)	0.001
rs7527192	60 (40)	81 (54)	9 (6)		75 (53)	62 (44)	4 (3)	0.042
rs2793378	60 (40)	65 (43)	25 (17)		62 (44)	62 (44)	17 (12)	>0.05
rs28362491	50 (27)	113 (69)	27 (14)		26 (22)	76 (63)	18 (16)	>0.05
rs696	26 (14)	130 (68)	34 (18)		23 (19)	74 (62)	23 (19)	>0.05
Asthma								
rs1136410	70 (38.8)	93 (51.6)	17 (9.4)		97 (86.6)	8 (7.1)	7 (6.2)	0.014
Allergic Rhinitis								
rs1136410	61 (47)	52 (40)	15 (11)		45 (43)	44 (42)	14 (13)	>0.05
rs2793378	50 (40)	59 (47)	15 (12)		44 (40)	54 (49)	11 (10)	>0.05
rs7527192	57 (44)	62 (48)	9 (7)		33 (32)	64 (62)	5 (5)	0.039

Grave's Disease								
rs28362491	50 (33.3)	80 (53.3)	20 (13.3)		40 (33.3)	63 (52.6)	17 (14.1)	>0.05
rs696	18 (12)	100 (66.7)	32 (21.3)		14 (11.6)	77 (64.2)	29 (24.2)	>0.05
rs7527192	60 (40)	81 (54)	9 (6)		71 (59.2)	40 (33.3)	9 (7.5)	0.0007
rs2793378	60 (40)	65 (43.3)	25 (16.7)		46 (38.3)	59 (49.2)	15 (12.5)	>0.05
Behcet's Disease								
rs28362491	50 (27)	113 (59)	27 (14)		43 (48)	38 (43)	8 (9)	0.003
rs696	25 (14)	130 (68)	34 (18)		18 (20)	38 (43)	33 (37)	0.033
WW:Wild Homozygote ins-ins for rs28362491, AA for rs696, TT For rs1136410, CC For rs2793378, GG for rs7527192								
WD:Heterozygote ins-del for rs28362491, AG for rs696, TC For rs1136410, CT For rs2793378, GA for rs7527192								
DD:Mutant Homozygote Del-del for rs28362491, GG for rs696, CC For rs1136410, TT For rs2793378, AA for rs7527192								

Table 1: Genotype assessment of SNPs rs1136410, rs7527192, rs2793378, rs28362491, and rs696 in PARP-1 and NFKB1 genes in autoimmune diseases in Turkish population.

Studies	**Controls**		**Patients**		**p**
	Alele,n (%)		**Allele,n (%)**		
Rheumatoid Artrit					
rs1136410	T,208 (63)	C,122 (37)	T,175 (68.4)	C,81 (31.6)	>0.05
Hashimoto's Thyroiditis					
rs1136410	T,215 (72)	C,85 (28)	T,227 (81)	C,55 (19)	0.013
rs7527192	G,201 (67)	A,99 (33)	G,212 (75)	A,70 (25)	0.03
rs2793378	C,185 (62)	T,115 (38)	C,186 (66)	T,96 (34)	>0.05
rs28362491	ins,213 (56)	del,167 (44)	ins,128 (53)	del,112 (47)	>0.05
rs696	A,180 (48)	G,198 (52)	A,120 (50)	G,120 (50)	>0.05
Asthma					
rs1136410	T,233 (64.7)	C,127 (35.2)	T,202 (90.1)	C,22 (9.8)	<0.000001
Allergic Rhinitis					
rs1136410	T,174 (68)	C,82 (32)	T,134 (65)	C,72 (35)	>0.05
rs2793378	C,159 (64)	T,89 (36)	C,142 (65.2)	T,76 (34.8)	>0.05
rs7527192	G,176 (68.7)	A,80 (31.3)	G,130 (63.7)	A,74 (36.3)	>0.05
Grave's Disease					
rs28362491	ins,180 (60)	del,120 (40)	ins,143 (59.6)	del,97 (40.4)	>0.05
rs696	A,136 (45.3)	G,164 (54.7)	A,105 (43.75)	G,135 (56.25)	>0.05
rs7527192	G,201 (67)	A,99 (33)	G,182 (75.83)	A,58 (24.17)	0.024
rs2793378	C,185 (61.67)	T,115 (38.33)	C,151 (62.92)	T,89 (37.08)	>0.05

Behcet's Disease					
rs28362491	ins,213 (56)	del,167 (44)	ins,124 (70)	del,54 (30)	0.004
rs696	A,180 (48)	G,198 (52)	A,72 (42)	G,104 (58)	>0.05

Table 2: Allele assessment of SNPs rs1136410, rs7527192, rs2793378, rs28362491, and rs696 in PARP-1 and NFKB1 genes in autoimmune diseases in Turkish population.

NFKB1 and PARP-1 as a Therapeutic Target for Diseases

Researchers have gained new insights into the relationship of DNA damage and autoimmune and inflammatory diseases regarding immune-related genetic factors. PARP-1 is included in the list of most important genetic factors for better understanding of the role of NFKB signaling. Both *human* and animal models may suggest a role for *inflammation, and effects of* genetic variations in the NFKB1 and PARP-1 genes may play a role in the pathogenesis of immune diseases. It is thought that in the NFKB1 and PARP-1 may **predisposition genes** and so abnormalities may yield multiple human pathologies regarding immune deficiencies and cancers [5,85].

Studies in recent years conducted on PARP-1 knockout mice and inflammatory related diseases have shown that PARP-1 inhibitors may prevent the progression or development of the disease [86,87]. Pharmacological inhibition of PARP-1 has provided benefits in rodent and large animal models of inflammatory disorders and this is widely accepted as an approach in the therapy of inflammatory diseases [88,89,17]. The most of inhibitors that have been in clinical trials for human use are aimed at cancer therapy [17,90]. According to the new therapeutic application of PARP-1 inhibitors, inflammatory disorders may have been treated with suitable chemical inhibitors of PARP enzymatic activity [89,91]. Persistent activation of PARP-1 may enhance tumourigenesis particularly in chronic inflammation or oxidation. Continuous PARP-1 upregulation in response to DNA damage causes inflammation/ROS-induced damage [85,92]. The PARP inhibitors can be applied to the patients to prevent and also treat cancer. Moreover, it is shown that tissue inflammation and injury events which are associated with spinal cord trauma, are reduced with PARP-1 inhibitors treatment [93].

Recent studies have shown that, it became the spotlight of the assessment of the genetic basis of inflammatory diseases through GWAS [94,95]. When we searched the published GWAS at recently, we noticed that PARP-1 rs1136410 was investigated in many diseases including narcolepsy, Alzheimer's disease, asthma, partial epilepsies, nephropathy, age-related macular degeneration, bipolar disorder, psoriasis, schizophrenia, Crohn's disease, UC, amyotrophic lateral sclerosis, prostate cancer, Type 2 diabetes, Breast cancer, Parkinson's disease, ischemic stroke, and RA. On the contrary, GWAS have not shown associations between the NFKB1 rs28362491 and inflammatory diseases in general, although some other studies have detected positive associations between NFKB1 and inflammatory diseases [24-26,72,85].

Understanding the relationship between these two genes and inflammation is critical to maintain the pretreatment with the inhibitors. There is obviously a molecular cooperation between these two proteins. Further genetic variation studies will increase our knowledge of the pathogenesis of the inflammatory diseases and cancer. Because of the pathogenetic role of NFKB1 and PARP-1 in various diseases, blockade of their inappropriate activations were expected to constitute a novel treatment strategy for the inflammatory disorder. It is worthy of note that PARP-1 and NFKB1 variation detection experiments and therapeutic approaches using the inhibitors may be demonstrated for improvement in the experimental therapy of systemic or tissue inflammation.

Up until this point, these observations indicate that the mechanism of PARP-1 and NFKB1 regulation differs between these autoimmune diseases. We aimed to provide a general update on studies about PARP-1 and NFKB1 gene variants that were most investigated in inflammatory diseases. Despite the lack of knowledge about several diseases which have not been investigated and so mentioned no polymorphisms yet, our study performed a systematic literature review to assess the relationships between NFKB1, NFKBIA, and PARP-1 SNPs and the risk of inflammatory disorders. Further studies regarding more genetic researches for PARP-1 and NFKB1 gene variants need to be investigated together for the full disclosure. It is important to study the assessments with response and resistance to therapy in order to identify variants in patients for a better therapy.

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