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REVIEW ARTICLE / DERLEME MAKALE

THE POSSIBLE RELATIONSHIPS BETWEEN SOME GENE POLYMORPHISMS AND SJOGREN'S SYNDROME

SJÖGREN SENDROMU İLE BAZI GEN POLİMORFİZMLERİ ARASINDAKİ OLASI BAĞLANTILAR

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ABSTRACT

Objective: *Sjögren's syndrome is a complex and widespread autoimmune disease whose pathogenesis is not fully elucidated and environmental and genetic factors affect the development of the disease. In order to reveal the effect of genetic contribution, studies have been conducted on the genes previously shown to play a role in other autoimmune diseases such as systemic lupus erythromatosus. In addition, two GWAS studies were conducted to investigate the role of more genes in the disease by screening the entire genome and the relationship of previously unknown genes with SS was shown.*

Result and Discussion: *Studies are being conducted with spontaneous and genetically modified animal models in order to better reveal the relationship between SS and genes and to reinforce the data obtained from humans. In this study, the relationship between the genes previously studied in other autoimmune diseases and the genes associated with SS in GWAS studies and the possible pathways that may contribute to the pathogenesis of the disease through related genes were investigated.*

Keywords: *Autoimmune disease, gene polymorphisms, genetic toxic effects, genotoxicity, Sjögren's syndrome*

ÖZ

Amaç: *Sjögren sendromu hala patogenezisi tam olarak aydınlatılamamış, hastalık gelişimini çevresel ve genetik faktörlerin etkilediği kompleks ve yaygın bir otoimmün hastalıktır. Genetik katkının etkisini ortaya koymak için daha önce sistemik lupus eritromatozus gibi diğer otoimmün hastalıklarda rolü gösterilen genler üzerinde bu genlerin SS ile ilişkisini ortaya koymak için çalışmalar yapılmıştır. Ayrıca iki GWAS çalışmasıyla da tüm genom taranarak daha fazla genin hastalıkta rolü incelenmiş ve daha önce SS ile ilişkisi bilinmeyen genlerin SS ile ilişkisi gösterilmiştir.*

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Sonuç ve Tartışma: *SS'in genlerle ilişkisini daha iyi ortaya koymak ve insanlardan elde edilen verilerin pekiştirilmesi için spontan ve genetiği modifiye edilmiş hayvan modelleriyle de çalışmalar yürütülmektedir. Bu çalışmada daha önce diğer otoimmün hastalıklarda incelenen genler ile GWAS çalışmalarında ilişkili bulunan genlerin SS ile ilişkisi, ilişkili bulunan genler üzerinden hastalığın patogenezisine katkısı olabilecek olası yolaklar irdelenmiştir.*
Anahtar Kelimeler: *Gen polimorfizmi, genetik toksik etkiler, genotoksisite, otoimmün hastalık, Sjögren sendromu*

INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune condition characterized by lymphocytic infiltration in exocrine glands such as saliva and lacrimal glands. Typical clinical findings in patients with SS due to progressive damage to exocrine glands are dry mouth (crestomyia) and dry eye (keratocongicivitis sicca). In SS patients, in addition to symptoms of dryness, extrraglandular signs such as Raynaud's phenomenon, fatigue, or arthritis are common [1-4]. Another feature of the disease is B cell hyperactivity. Major autoantibodies in SS target the intracellular antigens Ro52/TRIM21, Ro60/TROVE2 and La/SSB antigens, which are ribonuleoprotein-RNA complexes [5,6].

SS predominantly affects premenopausal women, and the incidence is 9: 1 in women compared to men [4,7]. It is known that SS occurs at 0.4-4.0% of the general population [4,8,9]. Modified European and American diagnostic criteria are the most commonly used diagnostic criteria in clinical practice [4,10]. According to this criterion, when it is accompanied by other rheumatoid diseases such as SLE or RA, it is classified as secondary SS (sSS) and SS alone is classified as primary SS (pSS). SS progresses with or without other autoimmune diseases [4,10,11]. Disease severity is determined according to ESSDAI (The EULAR SS disease activity index) [12]. Although mortality in SS is not different from the general population, quality of life in SS patients is significantly affected by reduced morbidity. SS patients are dependent on palliative methods in order to relieve major symptoms of crestomyia along with immunesuppressive methods. However, there are still no effective therapies to restore the SS process or to repair secretion dysfunction [4,13]. The risk of developing Non-Hodgkin lenfs B cell lymphoma is 44 times higher in SS patients compared to healthy individuals [4,14].

The etiopathology of the disease is unknown. It has been suggested that genetic factors, as well as exogenous agents such as Epstein-Barr virus (EBV), Hepatitis C (HCV) and human T-cell leukemia virus-1 (HTLV-1), hormones and microcremism may cause the onset of this disease [15].

SS' Relations with Genes

Genetic predisposition is one of the main features of autoimmune diseases [16,17]. SS is a genetically complex disease and little is known about the contribution of genetic factors to the disease. There are studies on monozygotic twins in other autoimmune diseases to investigate genetic contribution. In these studies, the comorbidity between disease and monozygotic twins was reported to be 25-40% in monozygotic twins [18]. However, there are no studies on monozygotic twins for SS. Case reports were made for case monozygotic and dizygotic SS twins only for SS. However, reliable correlation between twins is not evaluated in these presentations [19-21]. The incidence of other autoimmune diseases in the families of SS patients was reported to be 30-35%. Thyroid diseases, SLE and RA are the most common autoimmune diseases [22,23]. To date, gene studies on SS are included in the study of specific genes that may be genetic risk factors.

Candidate Genes

The first genetic studies of SS were carried out in genes that were previously known in the immune system and which had important functions or were shown to affect other autoimmune diseases such as romataid arthritis and systemic lupus erythromatosis (SLE).

In 1977, HLA genes were shown to be a risk factor for SS [24]. HLA (Human Leukocyte Antigens) complex is located on the short arm of chromosome 6 [25-27]. HLA antigens are expressed on many cell surfaces and have an important role in the recognition of antigenic stimulants, stimulation

of the immune system, and regulation of cellular and humoral immunity [26]. HLA complexes are classified into three classes as Class I, Class II and Class III [27].

HLA Class II proteins have the largest hereditary susceptibility to autoimmune diseases including SS. Reported risk haplotypes differ slightly from phenotype and race. The HLA-DR3 SS relationship was shown primarily in the white race, and the SS relationship of HLA-DR3-DQ haplotypes was shown in different ethnic groups [16,17,28-36] However, a meta-analysis identifies DRB1*0301, DQA1*0501, DQB1*0201, and DRB1*03 alleles as risk factors for SS, while identifying DQA1*0201, DQA1*0301 and DQB1*0501 alleles as preservatives [37]. Recently, a strong association between HLA-DRA, HLA-DQB1 and HLA-DQA1 and SS in 6p21 locus in a large study in Europe was reported [38]. In a study in China, HLA-DRB1/HLA-DQA1 in 6p21.3 locus and two independent signals associated with HLA-DPB1/COL11A2 [39]. Deterioration of autoreactive T cell tolerance through the presence of abnormal antigen demonstrates the key role of HLAs in autoimmune diseases. The disease relationship of HLA-suspected alleles is common in autoimmune diseases and different specific alleles and haplotypes are formed, different alleles direct targeting of specific autoantigens [40]. HLA Class II is associated with autoantibody production in SS, whereas anti-Ro/SSA and anti-La/SSB are significantly higher in HLA-DQ1/HLA-DQ2 heterozygous patients [41] but not related to other clinical features [32]. HLA-DRB1*1501-DRB1*0301 is associated with anti-ACA (anticyclic citrullinated antibodies) [42]. Amino acid variations in the hypervariable region (HVR) region of the HLA complex affect peptide binding and T cell presentation; The association of specific variations in binding wells 7 and 9 of HLA-DRB1 with changes in depth and polarity was shown in the Chinese population [35]. Although HLA Class I and HLA Class III genes were also studied in the following years, studies focused on HLA Class II genes.

On the other hand, polymorphisms in non-HLA genes, which have been shown to be associated with other autoimmune diseases, were also investigated in SS. One of the non-HLA genes is STAT4. STAT4 (signal transducers and activators of transcription-4) is an important transcription factor for the transmission of IL-12, IL-23 and Type 1 interferon-mediated signals involved in Th1 and Th17 differentiation, activation of monocytes and INFγ production [43-45]. STAT4 haplotypes have been shown to be a risk factor for the development of SLE and RA in the caucasians and its relationship with SS [46]. STAT4 polymorphism was investigated in different ethnic groups in different loci such as rs7574865 [47] and rs7582694 [48]. In these three studies, it was determined that rs7582694 polymorphism posed a risk for SS. This polymorphism was found to be poorly correlated with m-RNA levels of various interferon-induced genes in peripheral blood mononuclear cells of SS patients [48].

The distinctive feature of this disease is B cell hyperactivity. B cell hyperactivity was demonstrated by the presence of autoantibodies and hypergammaglobulinemia. The most risky group in development of lymphoma -especially non-Hodgkin's lymphoma- in all autoimmune diseases is pSS [49].

In addition, the association of BAFF (B-cell activating factor) polymorphisms in the development of other autoimmune diseases has been shown previously [49-55]. BAFF also known as B lymphocyte stimulator, is a member of the TNF superfamily that regulates the immune [56-58]. A cytokine facilitates B cell survival and maturation [56,58]. It is expressed as membrane bound (mBAFF) and soluble protein (sBAFF) [3,58-60]. Many cells are produced by antigen-presenting cells (B cells, monocytes/macrophages, dendritic cells (DC), plasmacytoid DC, follicular DC), epithelial cells, active T lymphocytes) [58,59]. In the presence of type 1 interferon (INFγ, LI-10, TLR3, TLR4, TLR9, etc.), BAFF expression increases [57,58,60]. Binding of BAFF to BAFFR triggers NF-κB (non-canonical nuclear factor κB) signaling [58,61]. The relationship of BAFF with overexpression with mature B cell hyperplasia and development of SLE and SS-like symptoms in lymphoid tissues has been previously demonstrated in experimental models [1,58,62].

It is thought that genetic variation of BAFF increases the risk of developing lymphoma [53,63]. It has been reported that various SNP (single nucleotide polymorphism) in various BAFF genes contribute to anti-Ro and/or anti-La positivity or high sBAFF level [64]. In addition, the association of the BAFF receptor with His159Tyr mutation, which causes deregulation of apoptosis by activation of the NF-κB pathway, has also been demonstrated [65]. It is also known that BAFF affects Type I and Type II interferon regulation and thus its contribution to SS development is bi-directional with its

contribution to B cell hyperactivity as well as its contribution to cytokine production. Studies on the effect of BAFF on both B cell and cytokine production showed a relationship between gene polymorphism and serum BAFF level, blood and salivary gland BAFF transcription level [66].

TNFAIP3 interacting protein 1 (TNIP1) encoded by the TNIP1 gene is an important signaling protein in the NF-κB pathway. Together with TNFAIP3 (Tumor necrosis factor alpha inducible protein 3), it acts together with the TNFAIP3 protein to suppress NF-κB activation. The association of TNIP1 gene polymorphism with many autoimmune diseases such as systemic sclerosis, rheumatoid arthritis (RA), psoriasis, SLE [67-76] was determined. In addition, its relationship with SS and anti-Ro/SSA and anti-La/SSB autoantibody seropositivity in SS were also shown [38]. On the other hand, the TNFAIP3 gene has been reported to be associated with diseases such as SLE and RA [66,77-79], and is also associated with pSS in GWAS studies. Allelic variations of the TNFAIP3 gene have been reported to be associated with pSS [80,81].

Thrombospondin-1 (TSP-1) is an adhesion matrix protein encoded by the THBS1 gene, which activates latent TGFβ and some anti-inflammatory cytokines and regulates extracellular and intracellular signaling complexes; expressed in the corneal epithelium, stroma and endothelium. Dry eye is one of the most important symptoms in SS. In this respect, the relationship between THBS1 polymorphism and SS has attracted attention and the relationship between THBS1gene variations and anisotropy and orientation symmetry coefficients of corneal nerve fibers has been shown [82]

None of the candidate genes reported for polymorphism in SS studies have changed the coding sequences of these genes, and only single SNPs have been studied in studies with the candidate gene approach.

GWAS Studies

Genome-wide association studies (GWAS) are a powerful molecular method that scans the entire DNA to determine the relationship between specific disease phenotypes and any loci. It yields SNPs associated with different polymorphic alleles covering the entire genome. GWAS studies are conducted in large patient and control populations, which is important, and allows a good comparison between races and to determine whether the observed relationship is race-bound. In addition, since these studies are clinically studied in a broad spectrum, the selection of participants is better [39].

Unlike other autoimmune diseases, there are only two GWAS studies for SS. One of them is found in the European population by over 10,000 participants. All patients were diagnosed with SS according to European-American Consensus Criteria. In this study, seven genetic regions were identified that could exceed the statistical threshold $p<5\times10^{-8}$, MHC-II loci, IRF5, STAT4, IL12A, BLK, CXCR5 and TNIP1. The strongest association was found in the HLA-II locus, followed by STAT4 and IRF5. The HLA-II locus, STAT4 and IRF5 were previously identified by the candidate gene approach, a stronger statistical value was obtained with this study, more samples were studied. IL12A, BLK and CXCR5 are important genes in immune signaling and their association with SS was demonstrated for the first time. TNIP1 is involved in the NFκB pathway and is a new gene associated with SS in the GWAS study. TNFAIP3, DGKQ, and FCGRN2 were found to be statistically poorly correlated. In this study, genes associated with SS are important genes in immune system functions [83].

The other GWAS study was performed in 1090 healthy and 597 SS cases in the Chinese population and 642,832 SNPs were detected. In this study, the strongest relationship was found in the GTF2I gene, which is a general transcription factor, and the other related genes are MHC-II, STAT4, and TNFAIP3 genes (Table 1) [84].

The results of these extensive studies conducted in two different populations show that there are differences and similarities between the European and Chinese populations. GTF2I polymorphism was observed only in Chinese population, while IRF5 polymorphism and other polymorphisms were not seen in Chinese population. The two important genes involved in the NFκB pathway were found to be related differently in both populations for TNIP1 and TNFAIP3. TNFAIP3 was found to be statistically significant in the Chinese population and weak in the European population. TNIP1 was associated only in the European population. These results indicate different genetic risks for both populations and should be confirmed in further studies.

Table 1. SS Associated Non-HLA genes in GWAS Studies [39]

Alleles with Gene	Function	Determination	References
STAT4	Transcription Factor	2	83
IRF5	Transcription Factor	1	83
IL12A	The cytokine	5	83
BLK	BLK B Cell Kinase	2	83
CXCR5	Chemokine	3	83
TNIP1	NFκB signaling	3	83
GTF2I	Transcription Factor	1	84
TNFAIP3	NFκB signaling	1	84

In these studies, none of the genes associated with SS were lacrimal and salivary glands, proteins associated with nerve conduction in these glands, secretion devices and X-crosomes. Associated genes are those related to immune system functions. Based on these results, it is seen that the immune system and the differences of activity in the immune system are the most important factors in the pathogenesis of SS.

Although the pathogenesis of SS is still unclear, the mechanisms that may contribute to the pathogenesis of the disease have been proposed based on candidate gene approach and GWAS related genes. The most common pathway is increased interferon signaling and cytokine production. The IRF5, STAT4, and IL12A genes contributing to this pathway were associated with SS in candidate gene approach and GWAS studies. The second possible pathway is B cell production, antibody formation and changes in antibody clearance. BLK, CXCR5 and FCGR2 are also related genes involved in these pathways and involved in these pathways. The third pathway is the NFκB pathway and the genes involved in these studies are TNIP1 and TNFAIP3 (Figure 1) [39].

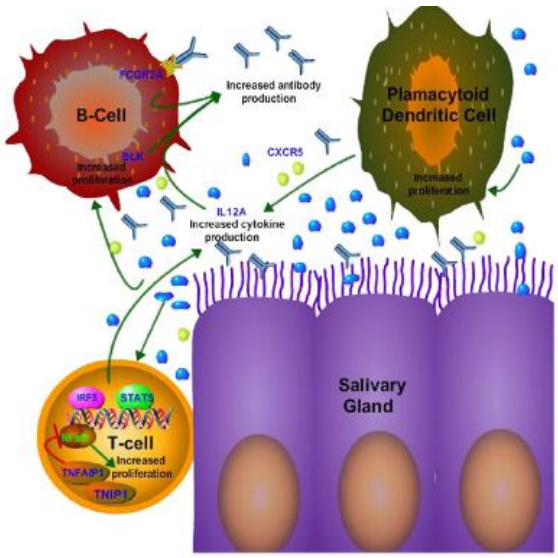

Figure 1. Functional changes in potential paths [39]

Functional Studies

All gene polymorphisms associated with SS were detected in non-coding sequences of the gene of interest. This led to gene studies to evaluate the effect of these polymorphisms on gene expression. In the GWAS study, mRNA expression level of some genes was compared in groups with and without polymorphism. Accordingly, if this polymorphism is found in the transcriptional regulatory region of

the gene, IRF5 and HLA-II gene expression levels are higher in SS patients, and related polymorphisms such as GTF2I have no effect on gene regulation [39].

Depression is a common condition in SS. In a study, the association of platelet serotonin levels with the serotonin transporter gene (5-HTT) polymorphisms in SS patients was investigated and it was reported that platelet serotonin levels were lower in the presence of intronic 5-HTTVNTRin2 (I/s) polymorphism compared to controls [85].

In another study, the relationship between the level of surfactant protein-D (SP-D) and SP-D genotype, which is thought to have an effect on the pathophysiology of the disease, was examined but no relationship was found between them [86].

Protein tyrosine phosphotase non-receptor type 22 (PTPN22) T cells, B cells, natural killer cells, DCs, monocytes and macrophages are expressed in many immune-related cells [87], regulate T cell receptor signaling [88]. PTPN22 in myoloid cells potential TLR-induced Type I interferon (IFN) production [89]. PTPN22 allelic variations are risk factors for many autoimmune diseases such as Type 1 diabetes, RA, SLE and hashimoto trodiditis [87-90]. Many PTPN22W-related diseases have been reported to be associated with impaired adaptive immunity and autoantibody production [88]. The frequency of phenotype PTPN22W* variation in pSS patients with low Type I INF blood levels was reported to be higher than controls and pSS errors with high Type I INF blood levels [91]. Gene variations of the F11R protein, which has many functions such as intracellular signaling, regulation of cellular permeability, stimulation of cell translocation during inflammatory processes, and cytokine production were investigated in SS. In this study, it was reported that some variations were associated with SS and F11R mRNA expression was lower in SS patients compared to healthy controls [92].

Animal Studies

In order to understand SS pathogenesis, human genotyping and genotype and phenotype compatibility studies are conducted concurrently with animal studies. Thus, the results obtained from humans and animals are compared and tried to prove the accuracy of the predicted mechanisms.

Animal models have been developed in order to understand the pathogenesis of SS and studies are being conducted on these models. Animal models are very valuable for elucidating pathogenesis and applying therapeutic approaches. Animal models are important especially in the absence of very clear clinical indicators at the onset of the disease and inability to detect changes in disease onset and help researchers to monitor changes that contribute to pathogenesis at the onset of disease [93]. The animals developed and used for this purpose are genetically similar to animals, such as mice and rats suitable for gene cloning and transgenic modification [94]. However, the data obtained from animal studies are limited in the elucidation of the disease due to factors such as developmental process between humans and mice, differences in adaptive and innate immune response and environmental conditions [95].

Spontaneous animal models allow for an understanding of the tendency or resistance loci of the disease, the time-related profile of disease formation and progression. Many spontaneous animal models used for pSS are derived from non-obese diabetic (NOD) mice. NODs develop not only Type 1 diabetes but SS-like autoimmune exocrinopathy. For this reason, SS is one of the most powerful tools for revealing the pathological mechanism [96]. Infiltration of the salivary and lacrimal glands occurs at 12-16 weeks of age. In addition, autoantibodies such as ANA, anti-SSA/Ro, anti-SSB/La and anti-M3R are also seen in SS patients [97,98].

In addition, genetically modified HTLV-1 tax transgenic (Tg) mouse, IL-6 Tg mouse, IL-10 Tg mouse, IL-12 Tg mouse, IL-14α Tg mouse, B-cell, to investigate the pathophysiology of SS-like diseases activating factor (BAFF) Tg mouse, retinoblastoma associated protein 48 (RbAp48) Tg transgenic mouse species and transforming growth factor beta 1 (TGF-β1) KO (knock out)mouse, inhibitor of differentiation 3 (Id3) -/- KO mouse, aromatase-deficient (such as Ar KO) mouse, phosphoinositide 3-kinase (PI3K) KO mouse and thrombospondin-1 (TSP-1) -deficient conjugate mouse are also used [99].

Some of the results from animal experiments are consistent with previous human studies. For example, IL-12 transgenic mouse model expressing both subgroups of IL-12 showed features similar to human SS such as increased SSB autoantibody production, decreased saliva flow, and lymphocytic

infiltration in glands [95]. In the GWAS study, the IL-12 gene is one of the genes associated with SS [39].

RESULT AND DISCUSSION

Despite the studies, the etiopathology of the disease is still unknown. Genetic factors, as well as exogenous and endogenous factors, have been shown to cause the onset of the disease.

Polymorphisms of the HLA, STAT4, BAFF and TNFAIP3 genes and the expression of these genes in tissues such as blood and salivary glands have been shown in the studies on the association of genes associated with SS in other autoimmune diseases such as romataid arthritis and SLE.

Again, two GWAS studies with larger populations showed the association of HLA, STAT4, IRF5, IL12A, BLK, CXCR5, TNIP1, GTF2I and TNFAIP3 genes and the expression of these genes in SS.

In these studies, mechanisms that could contribute to the pathogenesis of the disease were predicted from related genes. The most common of these is increased interferon signaling and cytokine production pathways. The second possible pathway is B cell production, changes in antibody formation and antibody clearance, and the third pathway is the NFκB pathway. Revealing the mechanisms that may contribute to the pathogenesis is very important in terms of contributing to the development of new drugs for the treatment of the disease.

In addition to human studies, gene polymorphisms which may be related to animal studies and appropriate animal models and the expression of this gene expression in tissues such as blood and salivary gland are compared with human studies and possible mechanisms are explained.

Although studies on suspected genes have shown that many genes may contribute to the pathogenesis of the disease, studies on genes that are not yet studied but that may be related to the disease should also be conducted. So far, gene studies are only SNP studies and there is a need for studies to determine multigenetic factors and to produce more powerful data in larger populations.

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

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