1. Introduction

Sjögren’s syndrome (SS) is the second most common systemic autoimmune disease (after rheumatoid arthritis, RA), with a prevalence of about 0.5% in the general population. It occurs primarily in perimenopausal women (at a ratio of women to men of 9:1) [1, 2]. Key features of the disease include infiltration of exocrine glands (predominantly salivary and lacrimal) by lymphocytes, production of inflammatory cytokines, and the activation of B lymphocytes and the production of autoantibodies. At the level of exocrine glands, loss of secretory activity has been observed leading to the characteristic symptoms of dry mouth and dry eyes. Other systems or organs such as musculoskeletal system (arthralgias, myalgias, and nonerosive arthritis of small joints), lungs, liver, skin, and kidneys can also be involved [3]. Compared to the general population, patients with SS exhibit significantly increased risk of developing B-cell lymphoproliferative disorders (usually B-cell lymphoma involving the mucosa-associated lymphoid tissue (MALT)), which affects about 5–10% of patients leading to significant increased morbidity and mortality rates of these patients [4]. Several clinical and laboratory manifestations have so far been proposed as adverse predictors for malignant disease and include features related to deposition of immune complexes (palpable purpura, peripheral neuropathy, low levels of complement C4, and cryoglobulinemia), swelling of the parotid glands, as well as high lymphocytic scores, and the presence of ectopic germinal centers in minor salivary gland biopsies [5]. The causative mechanisms of SS have not been fully elucidated. However, based on the current pathogenetic model, the interaction of both genetic, epigenetic [6, 7] and environmental factors seems to contribute to disease development [8]. Viruses, especially the Epstein-Barr virus (EBV) [9] and Coxsackievirus [10], hormones (low estrogen levels seen in perimenopausal women), stress [11], and occupational exposures [12] have been all considered as the main environmental triggers for disease onset. In the current review article, we will mainly focus on the contributory role of genetic influences in the development of the SS as well as in SS-related lymphoproliferation, a major disease complication.

2. Genetic Factors Associated with Sjögren’s Syndrome

Familial clustering and coaggregation with other autoimmune disorders in SS has been long considered [13–16]. In an Italian multicenter case control study [17], the risk of SS
development among first-degree relatives with autoimmune disease was sevenfold higher compared to controls. Of note, these first-degree relatives of SS patients had a higher risk of autoimmune disease compared to subjects without first-degree relative affected by SS. A large recent study in Taiwanese population confirmed previous observations showing that first-degree relatives of SS patients had an increased risk of SS development as well as of other autoimmune disorders, mainly systemic lupus erythematosus (SLE), RA, systemic sclerosis, and type 1 diabetes (T1D), compared to the general population [14]. Of interest, siblings of affected individuals demonstrated the highest relative risk for SS development compared to other first-degree relatives (parents and offspring), implying both genetic influences and shared environmental exposures as contributory factors to disease development [14].

Since the 1970s, strong associations between specific alleles of the major histocompatibility complex (MHC) and SS development have been suggested [18, 19]. Over the last decade, high throughput technologies allowed the confirmation of the dominant role of MHC alleles in the pathogenesis of the disease with novel genetic variants outside the MHC locus emerging as susceptibility factors [20]. The latter seem to be involved in signaling pathways of natural and acquired immunity, inflammatory responses and cellular apoptosis.

2.1. The Role of MHC Complex. Though initially recognized as major determinants of tissue rejection, MHC genes have been soon after appreciated as critical contributors to the pathogenesis of autoimmune disorders as well. They encode components of the human leukocyte antigen (HLA) system [21] including HLA class I (A, B, and C) and class II (DR, DQ, and DP), which present endogenous and exogenous antigens to T lymphocytes, respectively. MHC class II molecules, especially those which encode HLA-DR and HLA-DQ antigens, have been proposed as the most important genes associated with SS susceptibility. The first genetic study on SS revealed an association between SS and HLA-DR3 (which was in linkage disequilibrium (LD) with the class I allele HLA-B8) in Caucasian SS patients [22]. Subsequent reports highlighted the association between SS and the HLA-D locus [18, 23], with a diverse distribution between primary SS (high frequency of the alleles HLA-DRw3 and HLA-B8) and secondary SS (increased frequency of allele HLA-DRw4) [24], as well as in patients with SS characterized by the presence of Raynaud’s phenomenon (increased frequency of alleles HLA-DRw3 and HLA-DRw4) [25]. Subsequent studies in other ethnic populations confirmed HLA associations with SS susceptibility [26–41], with DRB1*04:05-DQB1*04:01 being a risk allele in Japanese populations [36], DRB1*08:03-DQB1*06:01 in Chinese populations [36], DR3 and DRII in Spanish populations [42], and DRB1*11:01, DRB1*11:04, DQB1*03:01, and DQA1*05:01 in Israeli Jews and Greeks [43, 44] (Summarized in Table 1). In a subsequent meta-analysis [21], HLA class II alleles DRB1*03:01, DQA1*05:01, and QBI*02:01 were shown to predispose to disease development, while DQBI*05:01 exhibited a protective role [21]. Two recent large genome wide association studies (GWAS), in Caucasian [45] and Han-Chinese population [46], confirmed the strong influence of HLA locus on SS. Further studies are required on the functional role of the HLA polymorphic regions in SS pathogenesis as well as their possible associations with disease diagnosis and/or prognosis.

A functional deletion of 6.7 Kb in the gene leukocyte immunoglobulin-like receptor subfamily A member 3 (LILRA3) has been also associated with autoimmune diseases. LILRA3 is a soluble receptor of class I MHC antigens involved in the regulation of immune function. It has been found in SS patients of both Caucasian [47] and Chinese [48] origin, as well as in other autoimmune diseases including multiple sclerosis [49], RA [50], and SLE [48].

2.2. Genetic Factors Associated with SS outside the MHC Locus.

In the following years, research has been directed to the investigation of single nucleotide polymorphisms (SNPs) in genes outside the MHC locus (summarized in Table 2 [51–68]), already found to be associated with other autoimmune diseases such as SLE [69]. These novel SS-associated genetic variants (outside the MHC locus) can be roughly classified into three main groups depending on the implicated signaling pathway [20]. The first group consists of variants in genes involved in the activation of the interferon (IFN) signaling pathway. The second group includes important genes affecting B-cell function and autoantibody production. Specific autoantibodies have been found in approximately two-thirds of SS patients and genetic contribution has been proposed. HLA class II SS-related phenotype has been associated with the presence of autoantibodies in various studies [33, 35, 40]. SNPs in the 5′ untranslated region of the BAFF [61] gene as well as in GTF2I [70] and genes implicated in the NF-κB pathway [45] have been also associated with the presence of autoantibodies. Finally, the third one contains apoptotic and inflammatory genes, which participate in the NF-κB signaling pathway.

2.2.1. Genes Associated with Interferon Pathways. Gene expression studies in SS patients over the last decade revealed upregulation of IFN-inducible genes (the so-called IFN signature) at the level of peripheral blood and affected salivary gland tissues in a substantial proportion of these individuals [71]. Moreover, recent data revealed that both type I (IFNα/β) and type II (IFNγ) IFN signatures are upregulated in both peripheral blood and minor salivary gland tissues derived from SS patients while the IFNγ/IFNα mRNA ratio in diagnostic salivary gland biopsies could predict the in situ lymphoma development in the setting of SS [72, 73]. While the mechanisms leading to this activation remain under investigation, several genetic variants in genes implicated in the IFN pathway have been designated as potential contributors [74].

Interferon Regulatory Factor 5 (IRF5). IRF5 is a transcription factor involved in type I IFN induction following TLR ligation [75]. Several polymorphisms of the IRF5 gene have been previously shown to either increase or decrease SLE susceptibility [74, 76]. Initial studies on SS revealed the IRF5 polymorphism rs2004640 (creates an alternate splice site (exon 1B) in the first exon) as predisposing factor
Table 1: Genetic associations of the HLA alleles with Sjögren’s syndrome susceptibility.

| Study                        | Year | Population          | Sample size (patients/controls) | Associated HLA alleles                          |
|------------------------------|------|---------------------|--------------------------------|-------------------------------------------------|
| Chused et al. [18]           | 1977 | American Caucasian  | 110 (19/91)                    | HLA-Dw3                                         |
| Fye et al. [22]              | 1978 | American Caucasian  | 115 (19/96)                    | HLA-Dw3-HLA-B8                                  |
| Moutsopoulou et al. [23]     | 1978 | American Caucasian  | 208 (24/184)                   | B lymphocytes immune response associated (Ia) antigens |
| Moutsopoulou et al. [24]     | 1979 | American Caucasian  | 206 (22/184)                   | HLA-Dw3-HLA-B8                                  |
| Manthorpe et al. [27]        | 1981 | Danish              | 32 (32/—)                      | HLA-Dw2                                         |
| Mann and Moutsopoulou [25]   | 1983 | American Caucasian  | 52 (25/27)                     | HLA-Dw3-HLA-B8                                  |
| Molina et al. [28]           | 1986 | American Caucasian  | 694 (68/626)                   | HLA-B8                                          |
| Moriuchi et al. [29]         | 1986 | Japanese            | 135 (21/114)                   | HLA-DRw3                                        |
| Vitali et al. [30]           | 1986 | Italian             | 90 (28/62)                     | DR3                                             |
| Papasteriades et al. [26]    | 1988 | Greek               | 218 (46/172)                   | DR-5                                            |
| Pease et al. [31]            | 1989 | British Caucasian   | 141 (41/100)                   | DR-3                                            |
| Morling et al. [41]          | 1991 | Danish              | 19 (19/—)                      | DQA1*0501-DQB1*0201-DQA1*0301                   |
| Kang et al. [36]             | 1993 | American Caucasian  | 210 (75/135)                   | DRB1*03-DRB3*0101-DQB1*0201-DQA1*0301           |
| Kang et al. [36]             | 1993 | Chinese             | 87 (45/42)                     | DRB1*0803-DQA1*0103-DQB1*0601                   |
| Kang et al. [36]             | 1993 | Japanese            | 82 (33/49)                     | DRB1*0405-DRB4*0101-DQA1*0301-DQB1*0401         |
| Roitberg-Tambur et al. [43]  | 1993 | Jews (Israel)       | 275 (17/258)                   | DQA1*001-DQA1*0201-DQB1*0501                    |
| Roitberg-Tambur et al. [43]  | 1993 | Greek               | 76 (22/54)                     | DQA1*0501                                       |
| Portales et al. [42]         | 1994 | Spanish             | 286 (30/256)                   | HLA-Cw7                                         |
| Wang et al. [32]             | 1997 | Chinese             | 206 (70/136)                   | DR3, DR52, DR2, DR5, and DR9                    |
| Jean et al. [38]             | 1998 | French              | 242 (42/200)                   | DRB1*1501*0301-DQB1*0201-0602                   |
| Rishmueller et al. [33]      | 1998 | Australian          | 244 (80/164)                   | DRB1*0605-DQB1*0501                             |
| Bolstad et al. [34]          | 2001 | Norwegian Caucasian | 95 (31/64)                     | DRB1*0403-03-DQB1*02-DQA1*0501                  |
| Nakken et al. [40]           | 2001 | Norwegian Caucasian | 210 (29/181)                   | DRB1*0301                                       |
| Anaya et al. [39]            | 2002 | Colombian           | 149 (73/76)                    | DRB1*0301                                       |
| Gottenberg et al. [35]       | 2003 | French              | 371 (149/222)                  | DRB1*03                                          |
| Manoussakis et al. [44]      | 2004 | Greek               | 301 (55/246)                   | DRB1*0301                                       |
| Kovács et al. [37]           | 2006 | Hungarian           | 98 (48/50)                     | DQB1*0201-DRB1*03-DQB1*0501                     |
| Cruz-Tapias et al. [21]      | 2012 | Meta-analysis       | 7636 (1166/6470)               | DQA1*0501-DQB1*0201-DRB1*0301-DQA1*0301-DQB1*0501 |
| Li et al. [46]               | 2013 | Chinese             | 5622 (1845/3777)               | HLA class II locus                              |
| Lessard et al. [45]          | 2013 | Caucasian           | 10916 (4712/6204)              | HLA class II locus                              |

Anaya et al. [39] reported on the genetic association of the HLA class II locus with Sjögren's syndrome (SS). This association was further explored in multiple studies conducted in Scandinavia and France, with consistent findings across different populations and study designs. The HLA-DQB1*03 allele was identified as a strong risk factor for SS, with increased frequencies observed in patients compared to controls. This association was also supported by a meta-analysis of multiple studies, highlighting the robust nature of the HLA-DQB1*03 association with SS.

Anaya et al. [39] also noted that there was a strong association between the insertion/deletion (in/del) of the CGGGG sequence in the IRF5 gene promoter and the development of SS. The insertion of an additional CGGGG unit (the 4×CGGGG allele) was associated with increased IRF5 transcription in peripheral blood mononuclear cells (PBMCs) and cultured epithelial cells derived from the salivary glands of SS patients, possibly through the addition of Sp1 binding site in the DNA region.
Table 2: Associations of non-HLA genetic locus with Sjögren's syndrome.

| Gene/chromosome | Polymorphism | Population                          | Sample size (patients/controls) | p value  | Relative risk | Study/year |
|-----------------|--------------|-------------------------------------|---------------------------------|----------|---------------|------------|
| IRF5/Chr7       | rs2004640    | Interferon pathways                 | 364 (210/154)                  | 0.01     | 1.93          | Miceli-Richard et al. 2007 [51] |
|                 | rs10488631   | Caucasians                          | 1079 (368/711)                 | 2.4 * 10^{-5} | 1.49          | Nordmark et al. 2009 [52] |
|                 |              | Norwegian/Swedish                   | 824 (385/439)                  | 6 * 10^{-6} | 2.00          | Miceli-Richard et al. 2009 [53] |
|                 |              | Caucasians                          | 1072 (540/532)                 | 5.5 * 10^{-6} | 1.70          | Nordmark et al. 2011 [54] |
|                 |              | Norwegian/Swedish                   | 1232 (120/1112)                | 0.01     | 1.47          | Korman et al. 2008 [55] |
|                 |              | Norwegian/Swedish                   | 1079 (368/711)                 | 0.0014   | 1.41          | Nordmark et al. 2009 [52] |
|                 |              | Colombian/German                    | 800 (277/523)                  | 7.7 * 10^{-6} | 1.40          | Palomino-Moraes et al. 2010 [56] |
| STAT4/Chr2      | rs7582694    | Norwegian/Swedish                   | 1072 (540/532)                 | 7 * 10^{-14} | 1.40          | Nordmark et al. 2011 [54] |
|                 | rs1068266    | Chinese                             | 5622 (1845/3777)               | 6.8 * 10^{-15} | 1.43          | Li et al. 2013 [46] |
|                 | rs1053577    | Caucasians                          | 1096 (4712/6204)               | 9.45 * 10^{-9} | 1.32          | Lessard et al. 2013 [45] |
|                 | rs13426947   | Caucasians                          | 1096 (4712/6204)               | 1.17 * 10^{-10} | 1.30          | Lessard et al. 2013 [45] |
|                 |              | Chinese                             | 1096 (4712/6204)               | 9.88 * 10^{-9} | 1.27          | Lessard et al. 2013 [45] |
|                 |              | French/Scandinavian                 | 1902 (1010/892)                | 0.0039   | 0.48          | Rusakiewicz et al. 2013 [57] |
|                 |              | Chinese                             | 378 (70/308)                   | 0.01     | 2.42          | Gomez et al. 2005 [59] |
|                 |              | French                              | 3.55 (183/172)                 | ns       | ns            | Ith et al. 2005 [58] |
|                 |              | Greek                               | 330 (193/137)                  | <0.001   | —             | Nossent et al. 2008 [61] |
|                 |              | Greek                               | 5622 (1845/3777)               | 1.31 * 10^{-5} | 2.20          | Li et al. 2013 [46] |
|                 |              | Norwegian/Swedish                   | 1072 (540/532)                 | 9.9 * 10^{-5} | 1.68          | Nordmark et al. 2011 [54] |
|                 |              | Norwegian/Swedish                   | 1072 (540/532)                 | 7.4 * 10^{-4} | 1.34          | Nordmark et al. 2011 [54] |
|                 |              | Chinese                             | 643 (250/393)                  | <0.05    | —             | Kong et al. 2013 [63] |
Table 2: Continued.

| Gene/chromosome            | Polymorphism | Population | Sample size (patients/controls) | \( p \) value | Relative risk | Study/year          |
|----------------------------|--------------|------------|--------------------------------|---------------|---------------|---------------------|
| TNFAIP3/chr6               | rs2230926    | Caucasians | (18/397)                       | 0.038         | 3.38          | Musone et al. 2011 [64] |
|                            | rs5029939    | Chinese    | 5622 (845/3777)                | 7.75 \times 10^{-5} | 1.67          | Li et al. 2013 [46]   |
|                            | rs6933404    | Caucasians | 10916 (4712/6204)              | 6.53 \times 10^{-8} | 1.26          | Lessard et al. 2013 [45] |
|                            | rs35926684   | Caucasians | 1025 (574/451)                 | 7.21 \times 10^{-8} | 1.26          | Nocturne et al. 2013 [65] |
|                            | rs2230926    | Caucasians | 1025 (574/451)                 | 0.01          | 3.36          | Lessard et al. 2013 [45] |
|                            | rs6579837    | Caucasians | 10916 (4712/6204)              | 3.30 \times 10^{-8} | 1.43          | Lessard et al. 2013 [45] |
|                            | rs7732451    | Caucasians | 10916 (4712/6204)              | 5.32 \times 10^{-7} | 1.34          | Lessard et al. 2013 [45] |
|                            | rs3792783    | Scandinavian/British | 5565 (1105/4460) | 3.4 \times 10^{-5} | 1.33          | Nordmark et al. 2013 [66] |
|                            | rs7708392    | Scandinavian/British | 5565 (1105/4460) | 1.3 \times 10^{-3} | 1.21          | Nordmark et al. 2013 [66] |
|                            | rs1800629    | Scandinavian/British | 5565 (1105/4460) | 1.6 \times 10^{-11} | —             | Nordmark et al. 2013 [66] |
| LTA/LTB/TNF gene clusters  | rs909253     | Norwegian/Swedish | 1060 (527/532)  | 4.42 \times 10^{-8} | —             | Bolstand et al. 2012 [67] |
| BAFF-R/Chr22              | His359Tyr    | Greek      | 427 (247/180)                 | 0.01          | 2.75          | Papageorgiou et al. 2015 [68] |
gene promoter of the 4R allele [53, 77]. Moreover, reovirus infection of salivary gland epithelial cells from SS patients carrying the 4R allele further increased IRF5 expression at mRNA level [53]. Taken together, these findings suggest a possible association between the IRF5 gene variants and the induction of type I IFNs (through the induction of the IRF5 gene expression after a viral infection) that could lead to the robust activation of the immune system in salivary glands (target organ) as an early event in SS pathogenesis.

Recent studies revealed genetic association of Transportin-3 (TNPO3), an IRF5 neighboring gene that encodes a nuclear receptor involved in the import of splicing factors in the nucleus, with both SLE and SS susceptibility with specific variants spanning the IRF5-TNPO3 locus being identified [45, 76].

**Signal Transducer and Activator of Transcription 4 (STAT4).** The transcription factor STAT4 is primarily involved in the signal transduction induced by the cytokines interleukin-12 (IL-12) and IL-23 leading to differentiation of T helper (Th) naïve cells towards a Th1 phenotype and subsequent production of IFN-γ [78]. STAT4 intrinsic variants, namely, rs7582694 and rs7574865, have been associated with SS development in four candidate gene association studies [52, 55, 56, 79]. Subsequent GWAS studies in SS patients with both European and Chinese descent confirmed STAT4 locus as an important determinant of SS susceptibility [45, 46]. While rs7582694 risk variant has been associated with increased expression of several IFN-inducible genes in SS patients [79], PBMC derived from lupus patients harboring the risk variant of rs7574865 demonstrated increased sensitivity to IFN-γ effects [78].

**Interleukin 12A (IL12A).** The recent GWAS in the Caucasian [45] but not Chinese population revealed an important association of IL12A gene polymorphisms with SS. The IL12A is a cytokine that forms a heterodimer with the IL12B subunit inducing through STAT4 the differentiation of naïve T-cells in Th helper 1 cells which promotes immune response through IFN-γ production by Th helper 1 cells [80].

**Natural Cytotoxicity Triggering Receptor 3 (NCR3).** NCR3/NKp30 is a natural killer (NK) specific receptor regulating the cross talk between NK and dendritic cells as well as type II IFN secretion [81]. The minor allele of the rs1575837 polymorphism within the promoter of NCR3 gene has been found as protective allele for SS development that is associated with reduced NCR3 gene transcription. Compared to controls, SS patients who lacked this polymorphism demonstrated higher circulating levels of the NCR3 ligand and demonstrated higher focus scores in salivary gland biopsy [57].

**Protein Tyrosine Phosphatase Nonreceptor 22 (PTPN22).** PTPN22 gene encodes the protein lymphocyte tyrosine phosphatase (Lyp) previously shown to be implicated in both adaptive (inhibition of T-cell receptor (TCR) and B-cell receptor (BCR) signaling) and innate immune responses (type I interferon (IFN) production by myeloid cells through TLR ligation) [82]. A single nucleotide polymorphism (SNP) of the PTPN22 gene 1858C>T (rs2476601) leading to substitution of arginine (R) by tryptophan (W) at position 620 has been previously shown to increase susceptibility to several autoimmune diseases including TID, SLE, and RA [83–85]. Although the underlying mechanisms leading to autoimmunity are not clearly delineated, a break in B- and T-cell tolerance through altered BCR and TCR signaling, enhancement of T helper follicular cells, and dampened type I IFN responses leading to a proinflammatory microenvironment have been all shown to contribute to autoimmune pathogenesis reviewed in [82].

In regard to SS, available data so far is rather conflicting. In contrast to a French report [58] in which no association with SS development was detected, studies in both Colombian [59] and Greek populations identified a strong association with SS susceptibility, particularly in patients characterized by low IFN signatures (manuscript in preparation). On this basis, we postulate that the apparent discrepancies between different studies are related to IFN status of SS patients included. This finding implies an additional shared etiological origin in autoimmune disorders, with a putative role of genetic contributors as determinants of distinct IFN patterns in patients with autoimmune diseases.

### 2.2.2. Genes Involved in B-Cell Function

**B-Lymphocyte Kinase (Blk).** The kinase Blk is a member of the src tyrosine kinase, which seems to be involved in signaling and differentiation of B lymphocytes [86]. Common polymorphisms in the Blk and in the neighboring family of the src tyrosine kinase, which seems to be involved in signaling and differentiation of B lymphocytes [86]. Common polymorphisms in the Blk and in the neighboring family of the src tyrosine kinase, which seems to be involved in signaling and differentiation of B lymphocytes [86]. Common polymorphisms in the Blk and in the neighboring family of the src tyrosine kinase, which seems to be involved in signaling and differentiation of B lymphocytes [86]. Common polymorphisms in the Blk and in the neighboring family with sequence similarity 167, member A (FAM167A) genes have been found to predispose to SLE [87], systemic sclerosis [88], RA [89], and recently SS [54, 60, 90]. Two main SNPs associated with SS development include rs12677843 (located in intron 1 of the Blk gene) and rs12549796 (second intron of FAM167A). These SNPs have been found in partial LD (r² = 0.29). The functional implication of these SNPs in SS remains unknown, although previous studies on SLE showed an association between the presence of risk alleles with decreased Blk mRNA levels and increased FAM167A mRNA levels in transformed B lymphocytes [87]. The association of Blk/FAM167A polymorphisms with SS was also suggested in a large GWAS study in Caucasian populations [45].

**B-Cell Activating Factor (BAFF).** BAFF is an important cytokine that promotes survival and proliferation of B-cells. Previously published data support a role for several haplotypes in the 5′ regulatory region of BAFF gene in autoantibody positive SS and increased serum BAFF levels [61] as well as in distinct (both low and high risk for lymphoma development) SS phenotypes [62].

**Chemokine (C-X-C Motif) Receptor 5 (CXCR5).** In a GWAS Caucasian study, chemokine receptor CXCR5 gene variants were found to confer protection against SS development [45]. The chemokine receptor CXCR5 detected in both circulating B-cells and activated CD4+ cells contributes to B- and T-cell migration in peripheral lymphoid as well as in inflamed peripheral organs, upon ligation with the CXCL13
chemokine [91, 92]. The latter has been previously found to be upregulated in salivary gland tissues derived from SS patients leading eventually to preferential retention of memory CXCR4+CXCR5+ B-cells in the SS derived salivary gland infiltrates [93].

**Early B-Cell Factor 1 (EBF1).** In a large candidate gene association study in SS patients of Scandinavian origin [54], genetic variants of the EBF1 gene (previously shown to be involved in antigen independent changes of B-cell differentiation [94]) have been found to confer increased risk for SS.

Ox40 Ligand/Tumor Necrosis Factor Superfamily 4 (Ox40L/ TNFSF4). Ox40L (or TNFSF4), a TNF family ligand member, expressed on activated dendritic cells, endothelial cells, and the B-cell surface, has been previously shown to get involved in B-cell activation through interaction with Ox40-positive T-cells [95, 96]. Genetic variants of Ox40L have been previously associated with susceptibility to SLE (in association with increased transcript and protein levels) and scleroderma, but not with primary biliary cirrhosis or SS after Bonferroni corrections in a Han-Chinese population [63, 97, 98]. However, in a Scandinavian study, two SNPs (namely, rs1234315 and rs1234314) located in the 5’-untranslated region of the gene Ox40L have been found to be significantly associated with SS [54].

General Transcription Factor 2I (GTF2I). An interesting finding from a large study (GWAS) in Han-Chinese [46] but not in European population revealed that a polymorphism in the GTF2I gene (namely, rs17026326) (encodes a transcription factor involved in both T-cell signaling [99] and activation of immunoglobulin heavy-chain transcription upon B-lymphocyte activation [100]) is strongly associated with SS development with overall risk (OR) scores higher than other SS-associated identified genes including MHC-II genes, STAT4, and TNFAIP3 [46]. This finding was also confirmed in another study in Chinese population and was linked to the presence of anti-Ro/SSA autoantibodies [70].

2.2.3. Genes Involved in the NF-κB Pathway

Tumor Necrosis Factor-Alpha Induced Protein 3 (TNFAIP3). TNFAIP3 gene encodes the A20 protein, an enzyme with ubiquitination activity that appears to play an important role in the regulation of inflammation through the NF-κB pathway. A20 protein is expressed at low levels on most of the cells but is rapidly induced after activation of NF-κB, acting as a negative feedback regulating both inflammation and apoptosis [101]. Experiments on mice revealed that A20 is important for survival and normal development since A20-deficient mice fail to regulate TNF induced NF-κB activation and die early due to multiorgan inflammation and cachexia [102]. Several genetic variants of the TNFAIP3 gene have been associated with autoimmune diseases including SS [64]. The coding TNFAIP3 polymorphism, namely, rs2230926, which changes the amino acid sequence from phenylalanine (Phe) to cysteine (Cys) at position 127 has been previously found to confer increased risk for SLE [103]. Functional analysis showed that the rs2230926 minor allele, which predisposed to disease, is less effective in inhibiting the activity of NF-κB after induction by TNF [103]. The association of TNFAIP3 rs2230926 polymorphism with SS has been recently confirmed by two large studies (GWAS) in both Caucasian [45] and Chinese population [46].

**TNFAIP3-Interacting Protein 1 (TNIP1).** Of note, polymorphisms of the TNIP1 gene, a molecule which interacts with the TNFAIP3 gene regulating the NF-κB activation, have been recently found to confer increased risk to SS [54, 66] and other autoimmune diseases [104, 105]. The role of TNIP1 polymorphisms in SS development was also confirmed in a large GWAS study in Caucasian population [45].

Lymph toxin Gene A (LTA). Polymorphisms of the lymph toxin gene A (LTA), located on locus LTA/LTB/TNF and related to the activation of the NF-κB pathway as well as inflammation, have been found to increase the risk of SS [67].

Chemokine (C-C Motif) Ligand 11 (CCL11). Finally, the CCL11 (eotaxin) is a chemokine with important role in SS. The expression of CCL11 has been found to be regulated by the NF-κB pathway and specific polymorphisms in the CCL11 gene have been associated with ectopic germinal center-like structures present in salivary gland tissues of a proportion of SS patients who are found to be at risk of lymphoma development [106].

2.3. Animal Models for the Study of Genetic Predisposition to SS. Animal models are useful tools for elucidating the etiopathogenetic mechanisms of various autoimmune diseases including SS. Over the last decade, various murine models have been proposed in an attempt to explore the early initiating and subsequent events leading to disease development. Spontaneous or transgenic murine models which are prone to develop Sjögren’s syndrome-like symptoms during lifetime include, among others (as reviewed recently in [107]), (NZB/NZW)F1, MRL, NOD, NOD-Aec1Aec2, Baff Tg, Opn Tg, and Act1<sup>−/−</sup>. The latter has been recently found to develop a disorder which closely resembles Sjögren’s syndrome in association with lupus. The Act1-deficient mice are characterized by marginal zone-like B-lymphocyte accumulations, salivary and lachrymal gland inflammation, and production of anti-Ro/SSA and anti-La/SSB autoantibodies [108]. Act1 is a negative regulator of BAFF and CD40 molecules (both implicated in B-cell survival and activation) while recent findings proposed it to be a critical component of the IL-17 signalling pathway [109]. Of interest, several SNPs around the TRAF3IP2 gene (which encodes the Act1 protein) have been recently found to confer increased risk to lupus and may play an important role in the induction of the interferon pathway (interferon-β, interferon inducible genes), which is relevant in the context of autoimmune diseases, like lupus and SS [110]. Taken together, these findings indicate the putative role of the SNPs in the TRAF3IP2 gene in the development of histological and serological features of SS.
2.4. Genetic Factors Associated with Sjögren's Syndrome Related Lymphomagenesis. Lymphocytic infiltration of the exocrine glands and ectopic formation of germinal centers have been considered as the sine qua non of lymphoma development. B-cell hyperactivity, the hallmark of SS, molecular events affecting B-cell function and survival, and the deregulation of the NF-κB pathway have been recently proposed as potential factors leading to lymphoma development [111]. Chronic antigenic stimulation of autoreactive B-cells and tumorigenic events such as chromosomal translocation and gene mutations/polymorphisms have been suggested as possible mechanisms underlying neoplastic diversion in the setting of SS. Regarding oncogenic mechanisms, the presence of the translocation t(14;18) (leading to overexpression of Bcl-2, an antiapoptotic gene promoting B-cell survival) has been detected in 5 of 7 salivary gland biopsies of patients with Sjögren's syndrome who developed lymphoma and in none of the 50 corresponding biopsies of patients with the syndrome not associated with lymphoma [112]. Furthermore, mutations of tumor suppressor gene p53 are possibly associated with the occurrence of lymphoma in patients with SS [113].

Additionally, somatic mutations and polymorphisms in the TNFAIP3 gene have been also reported in several types of lymphomas [114] including lymphomas of mucosal marginal zone (MALT), which is the major type of SS-related lymphoproliferative disease. In a recent study, the rs2230926 TNFAIP3 polymorphism along with other genetic alterations has been found to be associated with SS-related lymphoproliferation, especially of MALT type, while functional assays found that this polymorphism is associated with increased activation of the NF-κB pathway [65].

Another study failed to provide evidence for the presence of MyD88 L265P gene mutation (a nonsynonymous change at amino acid position 265 from leucine to proline (L265P)) in patients with SS with and without lymphoma [115]. MyD88 is an adaptor protein leading to NF-κB activation through TLR, IL-1R, and IL-18 signaling, which has been previously shown to be implicated in patients with Waldenström’s macroglobulinemia (WM) and other haematological malignancies [116, 117]. The absence of mutation in SS patients with or without lymphoma suggests that probably there are different pathogenetic mechanisms in lymphoproliferation in the setting of SS [115].

Given that deregulation of B-cell activation has been postulated as fundamental event in both autoimmunity and B-cell lymphomagenesis, the BAFF/BAFF-R axis attracted our research interest. Specific haplotypes of the BAFF gene could discriminate SS patients with lymphoma from SS patients without lymphoma and healthy controls [62] and a functional mutation His159Tyr of the BAFF receptor (BAFF-R), previously found to confer an increased risk in patients with NHL through activation of the alternative NF-κB pathway [118], has been found to be more prevalent in SS population compared to healthy controls. Of interest, more than two-thirds of SS patients complicated by MALT type NHL with an age at SS diagnosis between 3rd and 4th decade carried this mutation [68].

The role of known polymorphisms of the methylenetetrahydrofolate reductase (MTHFR), gene, an enzyme necessary for the DNA synthesis and methylation, which have been previously associated with NHL development [119, 120] and autoimmune diseases [121], has been also investigated. MTHFR polymorphisms have been found to be associated with both SS and SS non-MALT NHL development in association with methylation alterations, implying genetic and epigenetic abnormalities as common pathogenetic pathways in both benign autoimmunity and malignant transformation (Fragioudaki et al., in preparation).

3. Discussion/Conclusions

While growing evidence over the last years supports a genetic contribution to SS susceptibility, the majority of genetic variants seem to have weak or moderate effect (except, perhaps, for HLA locus), implying an additional role for the environmental insults such as viruses, hormones, and stress in disease pathogenesis. Given that the vast majority of these genetic loci have been also detected as susceptibility factors in other autoimmune disorders, shared mechanisms leading to deregulation of the immune system imply a central role in autoimmune pathogenesis. Heterogeneity of SS clinical expression from local disease confined to exocrine glands to lymphoma development should be always taken into account when genetic studies are designed, since distinct operating immune pathways underlie distinct clinical phenotypes. Further multicenter efforts exploring genetic, epigenetic, and environmental interactions are warranted to further clarify the pathogenesis of the syndrome.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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