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Genes and Sjögren's Syndrome

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Abstract

Sjoögren's syndrome (SS) is a chronic, progressive exocrinopathy characterized by infiltration and proliferation of lymphocytes into affected glands. Although patients are clinically identified through oral and ocular features, the full spectrum of disease encompasses a complex and myriad systemic symptoms. The primary pathophysiology includes concurrent mechanisms of dysregulated innate immunity and adaptive autoimmunity involving cell-mediated and humoral disease processes. Etiology involves environmental and genetic factors; however, large-scale genetic studies have not yet been conducted in SS and the genetic basis for SS is largely unexplored.

Although few genetic studies have been completed to date in SS, the overall evidence to support a genetic basis for SS continues to grow. Current data strongly suggest SS is a complex, polygenic disorder likely sharing common genetic determinants with related autoimmune diseases, such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Recent advances in SLE and RA provide valuable insight into the potential genetic complexity of SS. This article reviews association studies in various candidate genes for SS completed to date and highlights insights from SS mouse models. Advanced genetic and genomic technologies now are available for assaying gene expression and genetic associations across the entire genome, providing important opportunities to conduct unbiased interrogation of essentially every gene for a role in SS.

Keywords

Sjögren's syndrome; Genetics; HLA; Association

Genetic Epidemiology

SS is a common condition that disproportionately affects women by an odds ratio of more than 9:1 and usually presents during the fourth or fifth decade of life. Patients typically are classified as having primary SS (pSS) when additional autoimmune diseases are not evident or secondary SS (sSS) when a concurrent diagnosis of a well-defined autoimmune disease is

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recognized. Estimates of the prevalence of primary SS worldwide range from 0.2% to 3.39% (ie, 200–3390 cases/100,000 population); however, most estimates are closer to 0.5% to 0.7%.[1–6] Ethnic specific prevalence rates outside of European and North American cohorts have not been well defined. At present, there is no evidence to suggest temporal or geographic clustering of SS.

Similar to related autoimmune diseases, such as SLE and RA, susceptibility to SS likely is complex and results from variation in multiple genes.[1] Evidence for a genetic component often is derived from studies demonstrating increased concordance rates among monozygotic twins and familial aggregation. Several case reports of twins who had SS have been published, but reliable twin concordance rates have not been estimated.[7–10] Scofield and colleagues[10] reported a case of monozygotic twins who had SS and who had anti-60 kD Ro/SSA autoantibodies in their sera. In 2005, Houghton and colleagues[9] described a case of adolescent dizygotic twins who shared a diagnosis of pSS. One of the two sisters presented with pulmonary symptoms, uncommon in pediatric pSS. Given the many inter-relationships between SS and SLE and RA, twin concordance could be expected to be between those of RA (15%) and SLE (25%), with a female sibling or fraternal twin rate of 2% to 4% and estimated odds of female sibling concordance (λ_s) between 8 and 20.

Several families multiplex for SS have been described,[11–16] and family history with relatives having other autoimmune disease is common (30%–35%), often including SS (12%), autoimmune thyroid disease (AITD) (14%), RA (14%), and SLE (5%–10%).[14,17] In a pedigree of 60 members, eight were found to share a diagnosis of SLE. Among eight individuals who had SLE, all shared positive antinuclear autoantibodies, six shared pleuritis and malar rash, five reported photosensitivity, and four shared nephritis. Of the 51 relatives who contributed samples and for whom results were obtained, 29% had autoantibodies and 18% had autoimmune disease, including one who had SS.[16]

Related Autoimmune Diseases

In humans, clustering of autoimmune diseases such as SLE, RA, AITD, psoriasis, multiple sclerosis, and SS within families frequently has been documented.[18] Autoimmune serologic abnormalities are frequent (up to 55%, depending on the antibody specificity) in otherwise healthy family members.[19] Sharing of clinical and serologic features among related diseases also occurs. For example, subsets of patients who have SLE or SS may share similar symptoms (commonly including arthralgias, myalgias, fatigue, rashes, and visceral involvement from vasculitis) or serologic abnormalities, such as antinuclear autoantibodies, anti-Ro/SSA, or anti-La/SSB autoantibodies.[20] Some features of SS are shared more commonly with RA patients, such as arthritis and production of rheumatoid factor antibodies. Furthermore, in studies using high-density gene expression microarrays, the authors and colleagues have identified key disease pathways that are present in multiple disease phenotypes. For example, pathways known to be inducible by interferons (IFNs) are commonly dysregulated in certain subsets of patients across multiple autoimmune diseases, including SLE and SS.[21]

Several genetic loci are shown to be involved in the etiology of multiple autoimmune diseases in humans and support sharing of underlying disease mechanisms across related phenotypes. Associations of certain HLA loci with autoimmune diseases has been reported extensively in SS, SLE, RA, ankylosing spondylitis, psoriasis, multiple sclerosis, and type 1 diabetes.[22] A growing list of non-HLA genes also has been implicated in multiple autoimmune diseases. Examples include associations of cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) with AITD, type 1 diabetes mellitus (T1D), celiac disease, Wegener's granulomatosis, SLE, vitiligo, Addison's disease, and RA;[23–30] Programmed Death 1(PD-1)

with RA, T1D, and SLE;[31] and protein tyrosine phosphatase nonreceptor type 22 (PTPN22) with SLE, RA, T1D, Graves' disease, and Hashimoto's thyroiditis.[32–37] Interferon regulatory factor 5 (IRF5) and signal transducer and activator of transcription 4 (STAT4) are genes strongly associated with SLE for which there are recent data suggesting association in pSS.[38] Murine studies also are consistent with models of multigenic inheritance, and many susceptibility loci have been identified that are shared across different autoimmune mouse models for SS and other autoimmune diseases.[39]

Genetic Discovery in Sjögren's Syndrome

The advent of affordable, high-throughput genotyping technology has led to a surge in genetic discovery for complex diseases. Microarray-based platforms can now interrogate over 1 million markers of genetic variation in a single experiment and provide technical capacity for genome-wide association studies. This approach has been exceptionally fruitful for prostate cancer, breast cancer, and autoimmune diseases, such as T1D, RA, and SLE.[40–45] For example, more than 25 genes/loci in which genetic association with SLE is established are now recognized. Ongoing studies are expected to continue to reveal additional genes that contribute to SLE.

SS has been vastly understudied compared with related autoimmune diseases. A major contributing factor revolves around difficulties with patient classification and availability of multiple, large, independent cohorts of well-characterized patients for genetic studies. Ideally, assembly of cohorts for genetic studies involves multidisciplinary teams of investigators to ensure accurate, uniform phenotyping of oral, ocular, and systemic features of pSS. Classification issues have been addressed most recently by an international group on Sjögren's syndrome diagnostic criteria. Their efforts led to publication of an American-European Consensus Group report describing a revision of the 1993 European criteria.[46,47] A critical consequence of this classification scheme is that to be classified as having pSS, patients must have positive salivary gland histopathology or autoantibodies (anti-Ro/SSA or anti-La/SSB) with additional criteria in varying combinations. Labial salivary gland biopsies are not routine in clinical practice, which may lead to exclusion of a considerable number of patients who have classical clinical features of SS but who are seronegative for anti-Ro/SSA or anti-La/SSB.[48] Furthermore, misdiagnosis (particularly with SLE, RA, or multiple sclerosis) and underdiagnosis (many physicians fail to recognize or are not acutely familiar with SS) frequently occurs in routine clinical practice, making large-scale nationwide recruitment efforts problematic. In part because of these issues, there have been no reports of organized pSS genome scans.

Table 1 delineates the number of patient samples that are required to detect genetic associations of small effects and achieve 80% power using an additive genetic model. If the prevalence of SS is assumed to be 0.2% and the risk allele frequency (minor allele frequency) is 0.2%, then 4772 cases and 4772 controls are required to detect associations with an allelic odds ratio of 1.2 in a genome scan. However, 1785 cases and 1785 controls are required to detect associations for the same genome scan if the prevalence is assumed to be 0.5%. Candidate gene association studies in SS have only been conducted for approximately 20 loci to date, which is less that 0.1% of the estimated 20,000 genes in the human genome. Furthermore, studies published to date typically evaluated samples sizes of 200 cases/200 controls or fewer for association to a single or limited number of polymorphisms. Although candidate gene studies typically require smaller sample sizes because of the reduced number of independent statistical tests performed, independent replication of any genetic association is critical and remains to be accomplished for several of the genetic effects reported in pSS to date.

HLA Associations

Historically, HLA studies in SS dominated the literature before 1995. In humans, the 3.6-megabase (Mb) major histocompatability complex (MHC) region on chromosome 6 contains 140 genes between flanking genetic markers MOG and COL11A2.[49] The most well-characterized genes in the MHC region are the subset that encodes cell-surface antigen-presenting proteins. These genes, referred to as HLA genes, are well-documented risk factors for the development of autoimmune disorders.[50,51] As with most autoimmune diseases, associations of HLA loci (mostly class II genes) have been described and vary in different ethnic groups with SS.[1] In most studies, when an HLA association with pSS was demonstrable, a stronger association could be found to the anti-Ro/SSA and anti-La/SB autoantibody responses.

As shown in Table 2, HLA-DR and -DQ alleles represent the most common associations studied in SS.[14] The first HLA class II associations described were at the DR3[52–54] and DR2[17,54] loci in white populations. Together these two HLA sub-types were shown to account for up to 90% of the MHC association in patients who had SS.[17] These associations have been confirmed in the majority of subsequent studies evaluating northern European cohorts (see Table 2). In 2005, Anaya and colleagues[55] demonstrated that the HLA-DRB1*0301-DQB1*0201 haplotype was associated with pSS disease in Latin Americans. The possibility that both of these alleles play a role was reinforced in a 1998 study, which found the strongest disease susceptibility association with heterozygosity for DRB1*1501(DR2) and DRB1*0301(DR3).[53]

The HLA-DR3 haplotype, associated with SS and SLE, is within a region with extended linkage disequilibrium not observed other places in the genome. In general, linkage disequilibrium can be extinguished more than 30 to 60 kilobases (kb) in either direction. Graham and colleagues[22] found that the SLE risk region on DRB1*0301-containing haplotypes was no less than approximately 1 Mb. The risk haplotype containing DRB1*1501 (DR2), however, was much smaller and contained within approximately 500 kb. It is clear that haplotypes cooperate. In 1986, Harley and colleagues[65] reported that heterozygosity for DQw1 and DQw2 alleles are associated with high concentrations of anti-Ro/SSA and anti-La/SSB in pSS.

The HLA class I genetic associations with pSS are less powerful than the HLA associations at HLA-DR and HLA-DQ. Association with the HLA class 1 allele, B8, was first reported in 1975.[66,67] In 2001, Loiseau and colleagues[68] reported association with the HLA class 1 allele, A24. The results from this study showed that HLA-A24 is associated more often with DRB1*11-DQB1*0301 or DRB1*0301-DQB1*02 in pSS.

The evidence for association of some genes in the MHC, such as tumor necrosis factor (TNF)-α and the transporter 2, ATP-binding cassette, subfamily B (TAP2), may be stronger in patients who are seropositive for anti-Ro/SSA. Guggenbuhl and colleagues[69] analyzed TNF-α microsatellites in a group of 35 patients who had pSS and 146 healthy controls and found an association between joint symptoms or anti-Ro/SSA autoantibodies in patients who had pSS and TNF-α10. In contrast, Jean and colleagues[70] found no association between these two subgroups of patients who had pSS and TNF-α alleles. Polymorphisms of TAP2 gene, were studied in a collection of 108 Japanese patients who had SS and 160 controls. A formerly unknown TAP2 allele, Bky2, was found in increased frequency in patients versus controls ($P < .05$).[71] In addition, the level of anti-Ro/SSA autoantibody was significantly increased in patients carrying the Bky2 risk allele ($P = .001$).[71] This association was not confirmed in a cohort of 45 patients and 200 controls reported by Jean and colleagues.[70]

Non-HLA Associations

Evidence for association between SS and several non-HLA genes has been reported. These association studies have been performed in various populations, largely from outside the United States, and have involved small cohorts of patients who had SS (<200 cases). All reported non-HLA region associations and subsequent repudiations can be found in Table 3, some of which have been associated with pSS or various forms of sSS or specific autoantibodies.

Cytokine Polymorphisms

Cytokine gene polymorphisms in interleukin (IL)-10, IL-6, IL-1 receptor antagonist (IL-1RA), IL-4 receptor alpha (IL-4Rα), TNF-α, IFN-γ, and transforming growth factor-beta 1 (TGF-β1) have been associated with pSS (see Table 3). IL-10 is a cytokine produced primarily by monocytes that enhances B-cell proliferation and antibody production. In a study of 62 patients who had pSS and 400 healthy controls, Hulkkonen and colleagues[82,99] found that the IL-10 GCC haplotype was associated with pSS ($P = .011$). Using a collection of 108 patients who had pSS and 165 matched controls, however, Limaye and colleagues[83] were unable to confirm association with anti-Ro/SSA or pSS with IL-10 polymorphisms.

IL-6 also is involved in B-cell proliferation and antibody production. In a study of 66 patients who had pSS and 400 healthy controls, Hulkkonen and colleagues[82] found that IL-6 levels increased in parallel with the number of pSS criteria fulfilled. No genetic association, however, was found between IL-6 and pSS in a study of 129 French patients who had pSS and 96 healthy controls.[98]

The IL1RN*2 allele polymorphism of IL-1RA is believed to play a role in many autoimmune disorders. Perrier and colleagues[78] reported an increased frequency of the IL1RN*2 polymorphism in 36 patients who had SS relative to patients who had possible pSS. In addition, IL-1RA serum levels were elevated in patients who had SS compared with controls. Petrek and colleagues[73] genotyped IL-1RA in a collection of 39 patients who had SS and 76 healthy controls and observed no difference in the allele frequency of IL-1RA polymorphisms between cases and controls.

IL-4Rα gene has been evaluated in several studies for association in pSS. Youn and colleagues[79] observed an increased frequency of the Q551 allele in 45 Korean patients who had SS compared with 74 healthy controls. Another study demonstrated that patients who had pSS and carried the ARSPRV haplotype had an increase in the frequency of rheumatoid factor and other immunologic markers. In addition, a higher frequency of parotid gland enlargement in patients who had pSS was found in this study.[81] Meanwhile, the R576 polymorphism of IL-4Rα was not found associated with pSS by Lester and colleagues.[80]

Transforming Growth Factor-Beta 1

TGF-β1 has been implicated in the pathogenesis of pSS.[69] TGF-β1 is a profibrotic, immunosuppressive cytokine expressed by many cell types and is known to be under-expressed in salivary glands of patients who have SS compared with controls.[98] Gottenberg and colleagues[98] analyzed several cytokine gene polymorphisms, including TGF-β1, in a study of 129 French patients who had pSS and 96 controls. At codon 10 of TGF-β1, the frequency of allele C was elevated in patients who had pSS and anti-La/SSB autoantibodies and patients who carried the HLA-DRB1*3 haplotype. They hypothesized that the TGF-β1 polymorphism and the HLA-DRB1*3 haplotype act in combination to promote the production of anti-La/SSB autoantibodies.

Signal Transducer and Activator of Transcription 4

The most recently published association in pSS is with a single nucleotide polymorphism (SNP), rs7574865, found in the STAT4 gene.[38] STAT4 is a lymphocyte signal transduction molecule involved in IL-12 and IL-13 signaling.[38] STAT4, a member of the STAT family of transcription factors, encodes a protein that transmits signals induced by IL-12, type 1 IFNs, IL-23.33, and other cytokines. Upon activation by cytokines, STAT4 stimulates transcription of IFN-γ, a key inducer of T-cell differentiation into type 1 helper T cells. The protein encoded by STAT4 is required to regulate helper T-cell responses.[100,101] SNPs in the STAT4 gene also have been found strongly associated with SLE and RA.[102]

Interferon Regulatory Factor 5

IRF5, a member of a family of transcription factors, acts downstream of Toll-like receptors (TLRs) and type 1 IFN stimulation to promote the expression of proinflammatory cytokines, including IFN-α.[103,104] In a collection of 210 pSS cases and 154 healthy controls, a GT or TT genotype at the IRF5 SNP, rs2004640, was found in 87% of patients compared with 77% of controls (OR 1.93). The T allele results in the expression of the exon 1B isoform and significant over-expression of IRF5 in SLE cell lines.[105] This gene has been associated with SLE in genetic studies of Asian, white, Hispanic, and African American populations with several independent genetic effects within the IRF5 locus conferring risk.[106–112]

Protein Tyrosine Phosphatase Nonreceptor Type 22

PTPN22 is expressed primarily in lymphoid tissues. This gene encodes for the protein, Lyp, that dephosphorylates kinases, Lck, Fyn, and Zap-70, all known to have prominent roles in T-cell signaling. Moreover, this protein has a C-terminus binding site for Src tyrosine kinases (Csk) by which it functions to down-regulate T-cell signaling.[94] Lyp also binds the adaptor molecule, Grb2, leading to the negative regulation of T-cell signaling. In a collection of 70 pSS cases in Columbia and 308 matched controls, Gomez and colleagues[93] found the 1858 T allele a risk factor for SS (OR 2.42). After genotyping a collection of 183 pSS patient samples and 172 healthy controls, however, Ittah and colleagues[94] found no significant difference in the 1858 T allele frequency. Criswell and colleagues[18] also reported no association in their collection of 265 multiplex autoimmune families. The 1858 T allele of PTPN22 is associated with multiple autoimmune diseases, including T1D,[33] RA,[18,32,36,113,114] juvenile idiopathic arthritis,[114,115] SLE,[18,36,41,116] Graves' disease,[37,117] myasthenia gravis,[118] generalized vitiligo,[119] and Wegener's granulomatosis.[120] This allele has been shown to interrupt the interaction of Lyp and Csk, leading to aberrant activation of T cells.[94]

Cytotoxic T-Lymphocyte–Associated Antigen 4

CTLA4 is an important negative regulator of immune responses by T cells. CTLA4 contributes to maintaining peripheral tolerance and acts to suppress T-cell activation and proinflammatory cytokine production.[121] CTLA4 also can trigger apoptosis of activated T cells.[121] In 2006, Downie-Doyle and colleagues[121] genotyped 111 white patients who had pSS and 156 controls and reported association of CTLA4 +49G/A and CT60 haplotypes with susceptibility to pSS. Only months later, Gottenberg and colleagues[122] reported results from two separate cohorts of patients who had pSS and controls. In the first cohort of 142 patients who had pSS and 241 controls, allele frequency differences between patients and controls were observed for the CTLA4 + 49G/A allele (P = .036, OR 1.41) but not CTLA4 CT60. In a second cohort of 139 patients who had pSS, however, an insignificant allelic distribution was observed in CTLA4 + 49G/A and CT60 alleles between patients who had pSS and controls.[122] Inconsistencies between studies in part may be the result of analytic differences between haplotype versus single SNP analyses. The +49A:CT60G haplotype

also has been associated with SLE; however, association with additional haplotypes also has been observed but remains to be fully defined.[123,124]

Mannose-Binding Lectin

Mannose-binding lectin (MBL), a serum protein, is critical for host recognition of microorganisms. MBL contains a domain that can bind to the receptor collectin on the surface of phagocytes aiding in the phagocytosis of microorganism.[92] Another important function of MBL is to mediate the activation of the complement pathway by lectin.[92] A mutation in codon 54 of the MBL gene, in addition to other MBL polymorphisms, affects serum levels.[89] Using a collection of 104 cases of pSS in Japan and 143 healthy controls, Wang and colleagues[89] reported a higher allele frequency of wild-type MBL codon 54 in patients who had pSS than in controls ($P = .011$). Tsutsumi and colleagues[92] found homozygosity for the codon 54 mutation associated with pSS in a separate cohort of Japanese pSS cases and controls. Neither Mullighan[90] nor Aittoniemi[91] could confirm association between MBL polymorphisms and pSS.

FAS and Fas Ligand

FAS and FAS ligand (TNF receptor superfamily, member 6) have been implicated in the pathogenesis of various diseases of the immune system, including SS. These molecules are found on the cell surface and are responsible for transducing a death signal into the cytoplasm, leading to apoptosis.[74] Bolstad and colleagues,[74] upon genotyping a collection of 70 patients who had pSS and 72 healthy controls, observed significant differences in frequencies of three FAS alleles in patients compared with controls. Mullighan and colleagues,[75] however, did not find FAS alleles associated with SS in their collection of 108 cases and 101 controls.

Ro52

The anti-Ro52 autoantibody was discovered and demonstrated to be present in SS by Ben-Chetrit and colleagues.[125] A polymorphism in intron 1 of the Ro52 autoantigen also was shown associated with SS by Nakken and colleagues[95] in 97 patients who had pSS and were positive for anti-Ro/SSA compared with 72 healthy controls. Similarly, Imanishi and colleagues[96] reported a 7216A/G polymorphism in intron 3 that may influence the presence of anti-SSA/Ro52 antibody in patients who had pSS.

Immunoglobulin KM

Allotypes, originally defined by allospecific sera, are heritable differences in antibody structure and may contribute to genetic risk. In 1984, Whittingham and colleagues[86] discovered an association of anti-La/SSB autoantibodies with KM1 allotype in pSS. Twenty years passed before this discovery was replicated. Pertovaara and colleagues[126] found that anti-La/SSB autoantibodies occurred more frequently in patients who had pSS and the KM(1) allele than in those who did not have the allele ($P = .016$). No associations were observed between specific KM alleles and pSS or within anti-La/SSB subsets of patients who had SS in another study of comparable sample size.[87]

Other Associations

Other associations have been reported with pSS but have yet to be replicated (see Table 3). Upon genotyping a collection of 39 patients who had SS and 76 healthy controls, Petrek and colleagues[73] reported that polymorphisms of chemokine (C-C motif) receptor 5 (CCR5) may play a protective role in the development of SS. They found that the frequency of CCR5-delta 32/genotype was lower in patients than in controls.[73] Glutathione S-transferase (GST) MI and GSTT1 genes were investigated for association with SS in 106 Japanese

cases and 143 healthy controls. These studies showed that 57.5% of patients who had SS shared the GSTM1 homozygous null genotype compared with 44.1% of controls ($P = .035$). In addition, patients who had SS who shared the GSTM1 genotype were found to have higher levels of anti-Ro/SSA autoantibodies ($P = .0013$).[76] In a study of 63 white Finnish patients who had pSS and 64 healthy controls, the apolipoprotein E (ApoE) ε4 allele was found associated with early onset of pSS ($P = .047$).[72] Little is known about the function of minor histocompatibility antigen (HA-1). Harangi and colleagues[77] examined three white populations of patients who had pSS and healthy controls and determined that the HA-1 168 His allele frequency was lower in patients who had pSS than in controls ($P < .003$). Finally, Lawson and colleagues[97] observed a decreased frequency of the deleted/deleted genotype of the T-cell receptor beta variable (TCRβV) gene in patients who had pSS compared with controls.

Expression Profiling

Developments in high-throughput transcriptional profiling using microarray technology have dramatically enhanced the ability to characterize comprehensive patterns of gene expression in isolated cells from normal and diseased tissues. Gene expression profiling data in patients who have SLE and RA have demonstrated characteristic peripheral blood cell gene expression fingerprints or “signatures.” A prominent signature that has been observed repeatedly in autoimmune phenotypes is marked by overexpression of IFN-inducible genes.[21]

Several gene expression profiling studies in human SS have been reported and thus far have focused on salivary gland tissue and saliva. In a study by Hjelmervik and colleagues,[127] 10 patients who had pSS and 10 controls who had symptoms of SS but no objective criteria were evaluated. RNA was extracted from minor salivary gland tissue and hybridized to cDNA microarrays with features representing approximately 16,000 transcripts. Out of the top 200 most differentially expressed genes, the highest ranked transcripts were from the T-cell receptor β locus and many other genes indicating a chronic inflammatory state. Genes involved in IFN responses, such as increased expression of HLA class I and II and chemokines (eg, CXCL13) that attract lymphocytes to sites of inflammation, also were noted. In addition, down-regulation of the expression of carbonic anhydrase II, essential in saliva production and secretion, also was found, suggesting direct functional abnormalities in SS.

Using a similar study design, Gottenberg and colleagues[128] evaluated minor salivary gland tissue from seven patients who had pSS and seven controls using microarrays containing more than 10,000 probes. Analysis of these data also indicated IFN-mediated innate immune mechanisms in the pathogenesis of pSS. Specifically, 23 genes known to play a role in IFN signaling were identified, including two TLRs, TLR8 and TLR9. This study also demonstrated that plasmacytoid dendritic cells, a major producer of IFN, could be detected by immunohistochemistry in all patients who had SS but none of the controls. More recently, IFN-related gene expression patterns were reported in a third study of three pSS patients and three controls.[129] Furthermore, microarray studies by Hu and colleagues[130] have shown activation of IFN-related pathways is detectable in saliva. A proposed model suggests that stimulation of TLRs (eg, by viral or immune complexes) in salivary glands and downstream signaling pathways may be dysregulated, possibly because of genetic variants that predispose to SS, and that continual stimulation contributes to the persistence of what is observed as the IFN signature.[128] These studies strongly support the role of innate immunity, in addition to adaptive immune mechanisms, in the pathogenesis of SS. Additional studies using similar microarray technologies in saliva and peripheral blood is an

area of ongoing work, and holds significant promise for development of biomarkers for improved diagnostic and therapeutic approaches to SS.

Mouse Models

Animal models that resemble pSS are used to evaluate etiology and pathogenesis of SS. Several models have provided some insight into potential genetic contribution to clinical manifestations of the disease and are reviewed in detail elsewhere.[131] To date, there is no single mouse model that fully recapitulates the majority of cardinal disease manifestations of human disease. A large proportion of the approximately 20 models available, however, develop sialoadenitis or dacryoadenitis, so these models are particularly valuable tools for evaluating initiation of disease, various components of the overall SS phenotype, and the effects of immune manipulation. Those models that have been most characterized thoroughly or seem especially promising and for which genetic information is available that may aid in understanding human disease are highlighted.

The nonobese diabetic (NOD) mouse is an inbred strain that has been established as a model to study autoimmune T1D.[132] At 16 weeks of age, NOD mice spontaneously develop sialoadenitis and glandular dysfunction unrelated to the development of diabetes.[133] Diabetes and sialoadenitis develop independently in the NOD mouse. Various autoantibodies have been found in NOD mice, including those to alpha-fodrin, antinuclear antibodies (anti-Ro/SSA and anti-La/SSB), and antibodies to M3 muscarinic acetylcholine receptor.[134] Two genetic regions, Aec2 and Aec1, are essential for the development of SS-like disease; however, the precise gene/locus conferring risk is undefined.[131] NOD mice also carry a unique MHC haplotype ($H2^{g7}$) that is permissive for development of disease.

Several mouse models seem suitable for studying SS secondary to SLE.[131,135] The MRL/lpr strain carries a mutation in the lpr gene that impairs FAS expression, leading to apoptotic resistance in T cells. Mice develop B-cell hyper-reactivity, produce autoantibodies, and exhibit destruction of glandular tissue with loss of secretory function.[131] The NZB/W F1 mouse, also originally used as a model for human SLE, presents inflammatory infiltrates composed primarily of CD4+ T cells and some B and CD8+ T cells.[136,137] An increase in periductal laminin expression in the submandibular salivary gland of NZB/W F1 mice may result in the development of sialoadenitis.[138] Transgenic and knockout mice for TGF-β1, BAFF, and IL-14α also develop phenotypes with features of SLE and SS.[131]

Mouse models that seem to manifest phenotypes more reminiscent of pSS have been reported. In 1997, Saegusa and Kubota established the IQI/Jic mouse as a model for pSS. By 2 months of age, these mice develop infiltrating lymphocytes consisting of CD4+ T cells in small foci and B cells in large foci of the salivary glands.[139] Recent studies have suggested that expression of a tissue kallikrein 13 (klk-13) autoantigen in salivary glands may contribute to development of sialoadenitis in the IQI/Jic model.[140] Similarly, the NFS/sld mouse develops sialoadenitis that is characterized by inflammatory lesions containing CD3+ and CD4+ cells with few CD8+ and B cells. The mice carry an autosomal recessive gene, sld, and autoimmunity seems driven by reactivity against the cytoskeletal protein α-fodrin.[141,142] No anti-Ro/SSA or anti-La/SSB are detected, however, in the NFS/sld model.[143] Another model, the aly/aly mouse, carries an autosomal recessive alymphoplasia (aly) mutation mapped to a gene that codes for a nuclear factor κB–inducing kinase.[144] CD4+ T cells infiltrate the lacrimal and salivary glands at 3 months.[145] The major deficiency of the Aly/aly mouse is the lack of autoantibodies against nuclear elements or salivary glands, inconsistent with the serology of most human patients who had pSS.

Three promising new models for pSS include the Id3 knockout mouse and two inducible models. First, Id3 is a gene involved in T-cell receptor-mediated thymic selection at the time

of T-cell development. Mice deficient in Id3 develop anti-Ro/SSA and anti-La/SSB antibodies and dry eyes and mouth and experience lymphocyte infiltration in lachrymal and salivary glands.[146] After application of a CD20 monoclonal antibody treatment to Id3 knockouts, Id3 mice experienced sustained B lymphocyte loss. Recovery of salivary function and improvements of histopathology were observed.[147] Perhaps the Id3 knockout model for immunotherapy will translate successfully in patients who have pSS. Second, Fleck and colleagues[148] infected the C57BL/6-*lpr/lpr* mouse with murine cytomegalovirus and reported the development of acute and chronic sialadenitis. The persistence of salivary gland inflammation and high levels of anti-Ro/SSA and anti-La/SSB production resemble SS.[148] Finally, in 2005, Scofield and colleagues[149] introduced the BALB/c mouse immunized with Ro274 or Ro480 peptides from the Ro/SSA autoantigen. They reported the presence of infiltrating lymphocytes in these mice, reduced saliva production, and high-titer anti-Ro/SSA and anti-La/SSB.[149] The characteristics of this model most closely resemble pSS disease in humans. As with the majority of mouse models described for SS, dissection of the genetic loci that drive lymphocytic infiltration, aberrant cytokine production, development of autoantibodies, and glandular dysfunction will provide important tools for understanding human disease. Likewise, identification of causal genes in humans is necessary to fully inform the development of mouse models that more accurately represents human disease.

Summary

The evidence for a strong genetic component conferring susceptibility to pSS is mounting. Several associations with SS have been reported to date and provide evidence that the HLA region harbors important susceptibility loci and that multiple genes outside the HLA region play a role. Genetic discovery in SS, however, lags far behind the astounding success recently observed in other closely related autoimmune diseases. Full leveraging of the power of genome-wide association studies and other state-of-the-art genetic and genomic tools for discovery and replication of genetic factors in SS undoubtedly will require investigators to build large cohorts of well characterized patients. Genes involved in T- and B-cell function and innate immune mechanisms, such as IFN signaling, cytokine levels, and expression of autoantigens, all are likely important. Identifying the genetic factors that cause SS should provide fundamental new knowledge about this complex disease, allowing for more precise definition of pathogenic mechanisms leading to the overall SS phenotype and clinically heterogeneous subsets of patients. Critical opportunities are certain to follow for rapid translation into improved diagnosis and therapies for SS and its spectrum diseases.

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Table 1

Sample size requirements to detect genetic effects using 1, 100, or 1 million markers with 80% power

No. of Independent Tests	Percent Prevalence	Minor Allele Frequency (%)	Allelic Odds Ratio	No. of Cases	No. of Controls	*P* Value
1	0.2	0.2	1.2	940	940	0.05
1	0.5	0.2	1.2	352	352	0.05
1	0.2	0.2	1.5	195	195	0.05
1	0.5	0.2	1.5	100	100	0.05
100	0.2	0.2	1.2	2246	2246	0.0005
100	0.5	0.2	1.2	840	840	0.0005
100	0.2	0.2	1.5	465	465	0.0005
100	0.5	0.2	1.5	163	163	0.0005
1,000,000	0.2	0.2	1.2	4772	4772	0.00000005
1,000,000	0.5	0.2	1.2	1785	1785	0.00000005
1,000,000	0.2	0.2	1.5	980	980	0.00000005
1,000,000	0.5	0.2	1.5	345	345	0.00000005

The values in this table were obtained using the CaTS Power Calculator.

Data from Skol AD, Scott LJ, Abecasis GR, et al. Joint analysis is more efficient than replication-based analysis for two-stage genome-wide association studies. Nat Genet 2006;38(2):209–13.

Table 2
HLA associations with primary Sjögren's syndrome

Population	Polymorphism	Cases/Controls	Phenotype	Study
European	DRB1*1501/*0301	42/200	pSS	Guggenbuhl et al[56]
	DRB1*15	19/118	sSS	Mattey et al[57]
	DRB1*0301	29/181	pSS & anti-Ro52	Nakken et al[58]
	DRB1*0101	29/181	pSS & anti-Ro52	Nakken et al[58]
	DRB1*0501	29/181	anti-Ro52	Nakken et al[58]
	DRB1*03-DQB1* 02-DQA1*0501	62/64	anti-Ro with anti-La	Bolstad et al[59]
	DQB1*0201	29/181	anti-Ro52	Nakken et al[58]
	DRB1*0301-DRB3*0101-	73/135	pSS	Kang et al[60]
	DQA1*0501-			
	DQB*0201			
	DR3-DQA1*0501-	80/164	pSS with anti-La	Rischmueller et al[61]
	DQB1*02			
	DR2-DQA1*0102-	80/164	pSS with anti-Ro, no anti-La	Rischmueller et al[61]
	DQB1*0602			
Japanese	DRB1*8032/DQA1*0103/DQB1*0601	41/525	anti-Ro with anti-La	Miyagawa et al[62]
	DRB1*8032	41/525	anti-Ro with anti-La	Miyagawa et al[62]
	DRB1*0405-DRB4*0101-	33/49	pSS	Kang et al[60]
	DQA1*0301-			
	DQB1*0401			
Chinese	DRB1*0803/	42/43	pSS	Kang et al[60]
	DQA1*0103-			
	DQB1*0601			
European and African American	DQB1*0201-	67/00	anti-Ro	Scofield et al[63]
	DQA1*0101			
	(or –DQA1*0102 or DQA1*0103)			
Tunisian	DQB1 CAR1/CAR2	58/147	pSS	Hadj Kacem et al[64]

Table 3

Summary of non-HLA association studies in primary Sjögren's syndrome

				Positive Association		Negative Association	
Gene	**Site of Polymorphism**	**Allele or Genotype**	**Phenotype**	**Reference**	**Cases/Controls**	**Reference**	**Cases/Controls**
ApoE		ApoE ε4	Early-onset pSS	Pertovaara et al[72]	63/64		
CCR5		CCR5Δ32	pSS	Petrek et al[73]	39/76		
Fas	Nucleotide -671	G/G	pSS	Bolstad et al[74]	70/72	Mullighan et al[75]	108/101
	IVS2nt176	SNP C/T					
	IVS5nt82	SNP C/G					
GSTM1		Homozygous null genotype	pSS	Morinobu et al[76]	106/143		
HA-1	Nucleotide 1 500/504	168His	pSS	Harangi et al[77]	88/371		
IL-1RA	Intron 2	IL1RN*2	pSS	Perrier et al[78]	36/100	Petrek et al[73]	39/76
IL-4Rα		Q576R	pSS	Youn et al[79]	45/74	Lester et al[80]	98/164
						Ramos-Casals et al[81]	48/98
IL-10	Promoter-1082	SNP G/A	pSS	Hulkkonen et al[82]	66/400	Limaye et al[83]	108/165
	Promoter-819	SNP C/T					
	Promoter-592	SNP C/A					
	Promoter-1082, -819, -592	ATA/ATA		Origuchi et al[84]	47/107		
	Promoter-1082, -819, -592	GCC/ATA	Early-onset pSS	Font et al[85]	63/150		
Immunoglobulin KM		KM1	Anti-La in pSS	Whittingham et al[86]	26/1204	Downie-Doyle et al[87]	109/164
IRF5	Two from exon 1B	Rs2004640T	pSS	Miceli-Richard et al[88]	210/154		
MBL	Codon 54	Wild-type allele	pSS	Wang et al[89]	104/143	Mullighan et al[90]	97/106
						Aittoniemi et al[91]	62/400
		Homozygous mutant allele	Lupus, RA, SS	Tsutsumi et al[92]	266/129		
PTPN22	Nucleotide 1858	SNP C/T	pSS	Gomez et al[93]	70/308	Ittah et al[94]	183/172
						Criswell et al[18]	16/2064

				Positive Association		Negative Association	
Gene	**Site of Polymorphism**	**Allele or Genotype**	**Phenotype**	**Reference**	**Cases/Controls**	**Reference**	**Cases/Controls**
Ro52	Intron 1 (nucleotide 7216)	SNP C/T	Anti-Ro in SS	Nakken et al[95]	97/70		
	Intron 3 (137 from exon 4)	SNP A/G	Anti-Ro in pSS	Imanishi et al[96]	111/97		
STAT4	Intron 3	Rs7574865	pSS	Korman et al[38]	120/1112		
TAP2	Codon 577	TAP2*Bky2	pSS with anti-Ro	Kumagai et al[71]	108/160	Jean et al[70]	45/200
TCR-βV		Deletion/deletion	pSS	Lawson et al[97]	61/121		
TGF-β1	Codon 10	SNP C/T	pSS with anti-La	Gottenberg et al[98]	129/96		
TNF-α	TNF-α	TNF-α10	pSS with arthritis or anti-Ro	Guggenbuhl et al[69]	35/146	Jean et al[70]	45/200