Review

Genetic aspects of Sjögren's syndrome

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Abstract

Sjögren's syndrome is a multisystem inflammatory rheumatic disease that is classified into primary and secondary forms, with cardinal features in the eye (keratoconjunctivitis sicca) and mouth (xerostomia). The aetiology behind this autoimmune exocrinopathy is probably multifactorial and influenced by genetic as well as by environmental factors that are as yet unknown. A genetic predisposition to Sjögren's syndrome has been suggested on the basis of familial aggregation, animal models and candidate gene association studies. Recent advances in molecular and genetic methodologies should further our understanding of this complex disease. The present review synthesizes the current state of genetics in Sjögren's syndrome.

Keywords: apoptosis, autoimmune disease, candidate genes, cytokines, HLA

Introduction

Sjögren's syndrome is an autoimmune exocrinopathy of unknown aetiology. It is a member of the group of inflammatory rheumatic disorders classified as connective tissue diseases. Clinical experience indicates not only an overlap among these disorders but also a close relationship of, for example, autoantibody profiles [1]. The genetic implications of this overlap has not been extensively explored, and the genetics behind Sjögren's syndrome *per se* are not well characterized.

There is no single disease-specific diagnostic criterion for Sjögren's syndrome. For diagnosis, the most functional criteria are the recently modified European classification criteria, which include a list of exclusions [2]. In addition to the subjective symptoms of dry eyes and dry mouth, the following objective signs should be present: ocular signs by Schirmer's I test and/or Rose Bengal score; focal sialadenitis by histopathology; salivary gland involvement by either salivary scintigraphy, parotid sialography or unstimulated salivary flow; and autoantibodies of Ro/Sjögren syndrome antigen A (SSA) and/or La/Sjögren syndrome antigen B (SSB) specificity.

Sjögren's syndrome occurs worldwide and in all ages. However, the peak incidence is in the fourth and fifth decades of life, with a female : male ratio of 9:1. A number of studies have shown great variation in the frequency of Sjögren's syndrome (for review [3]). Prevalence studies have demonstrated that sicca symptoms and primary Sjögren's syndrome affects a considerable percentage of the population, with precise numbers dependent on the age group studied and on the criteria used [4]. A cautious but realistic estimate from the studies presented thus far is that primary Sjögren's syndrome is a disease with a prevalence not exceeding 0.6% of the general population (6/1000).

Although generally considered a T-cell-mediated disease, potential mechanisms underlying Sjögren's syndrome range from disturbances in apoptosis [5,6] to circulating autoantibodies against the ribonucleoproteins Ro and La [7,8] or cholinergic muscarinic receptors [9–11] in salivary and lacrimal glands in genetically predisposed individuals. Others relate reduced salivary and tear flow to aberrant glandular aquaporin-5 water channel proteins [12–14], although this is not unambiguous [15]. Possibly of greater importance is the recently described selective

HLA = human leukocyte antigen; IL = interleukin; LTR = long terminal repeat; MHC = major histocompatibility complex; NOD = nonobese diabetic; SSA= Sjögren syndrome antigen A; SSB = Sjögren syndrome antigen B.

downregulation of aquaporin-1 expression in myoepithelial cells in salivary glands in primary Sjögren's syndrome [16].

Genetic predisposition to Sjögren's syndrome

A genetic predisposition to Sjögren's syndrome appears to exist, and several families involving two or more cases of Sjögren's syndrome have been described [17–23]. However, the level of genetic contribution is not known. Because large twin studies in Sjögren's syndrome are lacking, the twin concordance rate cannot be estimated. Only a few case reports describing twins with primary Sjögren's syndrome are available [24–27]. Twins exhibited a very similar phenotype with almost identical clinical presentation, including dry eyes and dry mouth; similar serological data (IgG, IgM, IgA, C3, C4, antinuclear antibody, anti-Ro/SSA and anti-La/SSB, rheumatoid factor), with identical fine specificity in their immune responses to 60 kDa Ro/SSA; and identical labial salivary gland focus scores [24,27].

Familial clustering of different autoimmune diseases and co-association of multiple autoimmune diseases in individuals have frequently been reported [28]. Interestingly, it is common for a Sjögren's syndrome proband to have relatives with other autoimmune diseases (approximately 30–35%) [17,29,30]. Furthermore, Sjögren's syndrome exists in two forms – primary and secondary; the form that is present depends on whether it occurs alone or together with other connective diseases, such as systemic lupus erythematosus or rheumatoid arthritis [31]. Clustering of non-major histocompatibility complex (MHC) susceptibility candidate loci in human autoimmune diseases supports a hypothesis that, in some cases, clinically distinct autoimmune diseases may be controlled by a common set of susceptibility genes [32].

Sjögren's syndrome is considered a complex disorder. Susceptibility to the disease can be ascribed to an interplay between genetic factors and the environment. In complex diseases, one specific gene is neither necessary nor sufficient for disease expression. This makes the genetics behind these diseases more complicated than those of diseases with a simple Mendelian character.

Sjögren's syndrome is major histocompatility complex associated

The polymorphic MHC genes are the best documented genetic risk factors for the development of autoimmune diseases overall [33–35]. With regard to Sjögren's syndrome, the most relevant MHC complex genes are the class II genes, specifically the human leukocyte antigen (HLA)-DR and HLA-DQ alleles [36]. Patients of different ethnic origins exhibit different HLA gene associations [37]. In Caucasians of northern and western European backgrounds, including North American Caucasians, Sjögren's syndrome is among several autoimmune diseases that are associated with the haplotypes B8, DRw52 and DR3. The increased frequency of HLA-B8 was presumably due to an association with the HLA class II allele HLA-DRB1*03. However, a novel association of HLA class I alleles (i.e. HLA-A24) to susceptibility to primary Sjögren's syndrome was recently reported [38]. Beyond that, an association with DR2 has been found in Scandinavians [39] and with DR5 in Greeks [40]. All of the haplotypes are in strong linkage disequilibrium, resulting in certain difficulties in establishing which of the genes contains the locus that confers the risk. DQCAR is a very polymorphic CA repeat microsatellite located between the HLA DQA1 and DQB1 gene and specific DQCAR alleles have been found to be in tight linkage disequilibrium with known HLA DR-DQ haplotypes. HLA-DQB1 CAR1/CAR2 allele frequencies were found to be significantly different in patients with Sjögren's syndrome as compared with healthy control individuals in a study in which the Kaplan criteria were used to classify Sjögren's syndrome [41].

Apparently, the HLA haplotype may influence the severity of autoimmune disease. It has been claimed that Sjögren's syndrome patients with DQ1/DQ2 alleles have a more severe autoimmune disease than do patients with any other allelic combination at HLA-DQ [42], and the DR3-DQ2 haplotype has been indicated as a possible marker for a more active immune response in Finnish patients with Sjögren's disease [43].

HLA is associated with the presence of Ro and La autoantibodies in Sjögren's syndrome

Distinct HLA haplotypes have been associated with certain degrees of autoantibody diversification in Sjögren's syndrome [44]. Autoantibodies to Ro/SSA and La/SSB have been found to be associated with DR3, DQA and DQB alleles [45–47]. A dose-dependent contribution of DQα-34Q and DQβ-26L, in addition to the DRB1*03-DQB1*02-DQA1*0501 haplotype encompassing the transethnically associated DQβ-DI motif, represented the strongest contributors to the formation of an anti-Ro/La response in Norwegian patients with Sjögren's syndrome [45]. A stronger correlation has been found between anti-Ro/SSA autoantibodies and DR3/DR2 than that with the disease itself [45,48–50]. In Japanese persons, HLA class II allele association has been reported to differ among anti-Ro/SSA-positive individuals according to the presence or absence of coexisting anti-La/SSB [51].

Cytokine polymorphisms in Sjögren's syndrome

Cytokines serve to mediate and regulate immune and inflammatory responses, and have been implicated in the pathogenesis of a variety of autoimmune diseases, including Sjögren's syndrome. Numerous investigators have attempted to analyze the association of primary Sjögren's syndrome with cytokine polymorphisms, but at present no convincing relationship has been identified (for review [52]).

Both human and animal studies indicate the involvement of IL-10 in the pathogenesis of primary Sjögren's syndrome [53] and mice transgenic for IL-10 develop a Fas-ligand-mediated exocrinopathy that resembles Sjögren's syndrome [54]. A recent study described an association between primary Sjögren's syndrome and IL-10 promoter polymorphisms in a cohort of Finnish individuals, and a specific haplotype was found to correlate with high plasma levels of IL-10 [55]. Conversely, no association was found for IL-10 promoter polymorphism and primary Sjögren's syndrome or the presence of Ro autoantibodies in an Australian cohort of primary Sjögren's syndrome patients [56].

The IL-1 receptor antagonist regulates IL-1 activity in inflammatory disorders by binding to IL-1 receptors and thus inhibiting the activity of IL-1. The human IL-1 receptor antagonist gene (i.e. *IL1RN*) has a variable allelic polymorphism within intron 2 as a result of variation in number of an 86-base-pair sequence repeat [52]. An increased frequency and carriage rate of the IL1RN*2 allele has been found in primary Sjögren's syndrome [57]. No statistically significant association can be ascribed to tumour necrosis factor-α and primary Sjögren's syndrome [58].

Additional candidate gene studies

Because there is no disease-specific criterion for Sjögren's syndrome, the candidate genes studied may be related to other autoimmune phenotypes also. Mutations in the apoptosis genes have been identified as a possible cause or a contributing factor to human diseases [59], and the role of apoptosis has also been a major topic in autoimmune diseases, including primary Sjögren's syndrome (for review [5,6]).

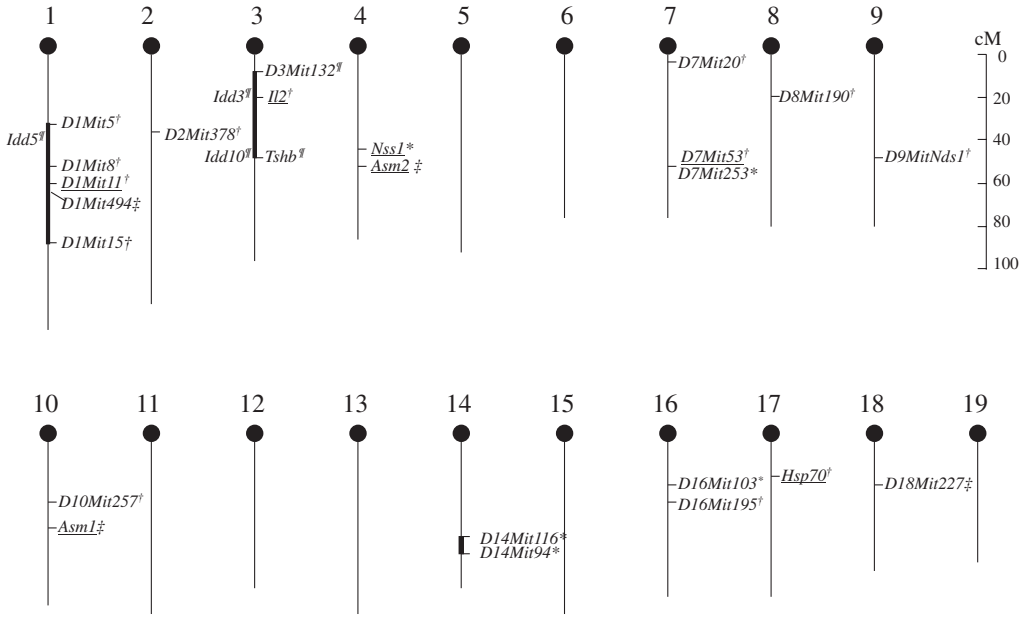
An increased frequency of apoptosis in ductal epithelial cells of the salivary glands leading to reduced salivary flow has been proposed as a possible disease mechanism [60,61]. Other investigators have suggested that inflammatory mononuclear cells are able to escape apoptosis because of defects in the death signalling pathway, which lead to accumulation of lymphocytes to displacement of functioning acinar cells [6,62]. In the complex cascade of apoptotic signal molecules, Fas and Fas ligand are central actors. An insert of a retrotransposon in the *Fas* gene was discovered in the murine model MRL/lpr-lpr, which exhibits progressive focal sialadenitis, and has as such been forwarded as a possible explanation for aberrant apoptosis in that experimental model [63–66]. This finding led to speculation over whether a similar phenomenon may be present in the human *Fas* gene. Now, more than 20 distinct *Fas* mutations are known in humans, and mutations in this gene have been identified as cause of or factor contributing to human diseases, such as autoimmune lymphoproliferative syndrome type I (for review [59]). Polymorphisms in the *Fas* and *FasL* genes have also been found in primary Sjögren's syndrome [67]. However, none of the polymorphisms in *Fas* or *FasL* entailed amino acid changes in patients with primary Sjögren's syndrome, and at present there exists no clear-cut mutation or defect in these genes that is clearly associated with primary Sjögren's syndrome and as such can be regarded as a disease-determining factor. Notably, the apoptosis cascade is built up of a huge number of signal molecules, and the possibility that there should be polymorphisms or mutations of vital importance for development of the disease among these factors still exists. Thus far, however, a definite role for apoptosis in primary Sjögren's syndrome cannot be confirmed.

The contribution of Ro/SSA and La/SSB in Sjögren's syndrome is not fully understood. It is not known how tolerance breakdown and autoantibody response to Ro/SSA and La/SSB is generated. The ribonucleoproteins are endogenous proteins that are normally hidden from the immune system, and should subsequently not give rise to abnormal B-cell responses. However, stress such as ultraviolet radiation, viral infections and apoptosis have been suggested to lead to undesirable cell surface exposure of autoantigens to the immune system [7]. Ro/SSA and La/SSB have been demonstrated in surface blebs of apoptotic ultraviolet-irradiated keratinocytes, implying a role in systemic lupus erythematosus [68]. Not much is known from a genetic point of view, but an association study has been performed in *Ro52* [69]. A single nucleotide polymorphism in intron 3 of the *Ro52* gene was found to be strongly associated with the presence of anti-Ro52 autoantibodies in primary Sjögren's syndrome [69]. This is interesting because alternative mRNA is made by deleting exon 4, which encodes a putative leucine zipper domain, to generate a shorter version of the Ro52 protein [70].

Genes that encode transporters associated with antigen processing (i.e. TAP genes) have also been associated with susceptibility to Sjögren's syndrome [71]. Others have indicated a putative role for the cysteine-rich secretory protein 3 (CRISP-3) gene as an early response gene that may participate in the pathophysiology of the autoimmune lesions of Sjögren's syndrome [72].

A 44-fold increased risk for the development of B-cell lymphoma has been documented in Sjögren's syndrome, and a role for activated B cells has been implicated [73]. Notably, it is not known whether B-cell activation is a primary cause or a secondary manifestation in Sjögren's syndrome. Patients are known to have increased levels of serum IgG [3]. Although the cellular basis of this hypergammaglobulinaemia and the strong associations of certain autoantibodies with particular MHC class II molecules have been intensively examined, little is known about the usage of IgV (immunoglobulin variable) region genes, and especially by autoantibodies in autoimmune diseases.

Figure 1



Chromosomal map illustrating the location of identified quantitative trait loci associated with sialadenitis development in various murine models. Chromosomal positions are based on the map from the Jackson Laboratory (http://informatics.jax.org/). Sialadenitis susceptibility loci are drawn from *[78], ¶[82], †[83] and ‡[84]; markers with LOD score >3.3 are underscored, however, for the markers *Il2*, *Asm2* and *Hsp70* a LOD score >3.3 was only obtained in females and for the marker *D1Mit153* only in males.

Therefore, a study of IgV_λ light chain gene usage in primary Sjögren's syndrome patients was undertaken by Kaschner *et al*. [74]. Those investigators identified molecular differences from controls in V-J recombination and concluded that disturbed regulation of B-cell maturation with abnormal selection, defects in editing immunoglobulin receptors and abnormal mutational targeting may contribute to the emergence of autoimmunity in Sjögren's syndrome.

Rheumatoid factors are autoantibodies against antigenic determinants that are present on the Fc portion of human IgG, and are found in sera and saliva of 60–80% of patients with primary Sjögren's syndrome [3]. We found rheumatoid factor to be present in sera of 91% of Norwegian anti-Ro-positive patients with primary Sjögren's syndrome [45]. The genetic origin and the mechanisms underlying its generation have been investigated in primary Sjögren's syndrome [75]. In such patients, rheumatoid factor used diverse V_H region genes, the majority of which show no evidence of somatic hypermutation, whereas light chain variable (V_L) sequences exhibited a moderate contribution of somatic hypermutation [76].

Understanding primary Sjögren's syndrome in view of animal models

An appropriate animal model of Sjögren's syndrome could greatly advance our ability to identify the target antigens, characterize the immune mechanisms and define the genetic background. Several animal models, both experimentally induced and spontaneous inflammatory reactions with features of human Sjögren's syndrome, have been reported and previously reviewed [77].

The nonobese diabetic (NOD) mouse develops a disease that mimicks human type 1 diabetes mellitus and has been intensively studied for this phenotype. It also spontaneously develops sialadenitis and several other features of Sjögren's syndrome, including autoantibodies against Ro/SSA [77]. The NOD mouse carries the MHC $H2^{g7}$ haplotype. In order to study the importance of NOD non-MHC genes, an $H2^{q}$ congenic NOD mouse, namely NOD.Q, was established [78,79]. Recently, a gene segregation experiment was conducted in a $(NOD.Q \times B10.Q)F_2$ cross, and genetic mapping revealed one locus (*Nss1*) associated with sialadenitis on chromosome 4 (LOD score 4.7; Fig. 1) [78]. The $H2^{g7}$ haplotype was not critical for sialadenitis development in the NOD background because the NOD.Q mouse also developed sialadenitis. The genetic control of sialadenitis appeared to be unique in comparison with diabetes and arthritis, because no loci associated with these diseases have been identified at the same location [79]. This supports earlier findings that the sicca syndrome occurs independently of autoimmune diabetes, and NOD MHC $I\text{-}A^{g7}$ was not essential for exocrine tissue autoimmunity [80].

More recently, alleles from chromosomes 1 and 3 of NOD mice have been found to combine to influence Sjögren's syndrome-like autoimmune exocrinopathy [81], and two intervals contribute synergistically to the development of Sjögren's syndrome on a healthy murine background; this has also been demonstrated in the NOD mouse after crossing (Fig. 1) [82]. Very recently, chromosome 1 was reported to be a major susceptibility region for development of autoimmune sialadenitis [83]. In different matings of NOD mice, including a (NOD × C57BL/6 [B6])F_2 cross, a (NOD × NZW)F_2 cross, and a ([NOD × B6] × NOD) backcross, an association with the middle region of chromosome 1 was detected in all crosses.

The NZB, MRL/*lpr*, NOD and NFS/*sld* strains are all experimental murine models that spontaneously develop salivary gland inflammation, of which the MRL/*lpr* and the NOD strains present with serum anti-Ro/SSA antibodies. An insertion of an *ET*-transposon in the *Fas* gene has been found to be responsible for the *lpr* genotype in the MRL/*lpr* mouse [65]. Similar *Fas* gene insertions could not be traced in Sjögren's syndrome patients [67]. A genome-wide scan of MRL/*lpr* mice revealed four susceptible loci, mapped on chrosome 10, 18, 4 and 1, which were recessively associated with sialadenitis [84]. The sialadenitis in MRL/*lpr* mice is probably under the control of polygenic inheritance, because the loci manifested an additive effect in a hierarchical manner. The different susceptibility loci reported for sialadenitis are outlined in Fig. 1.

Transgenic mice have frequently been used as models to study the role of viruses in the pathogenesis of a variety of diseases and to determine the importance of cytokines such as IL-10 [54]. Transgenic expression of IL-10 induced apoptosis of glandular tissue and promoted infiltration of lymphocytes. Transgenic mice containing the human T-cell lymphotropic virus type-1 *tax* gene under the control of the viral long terminal repeat (LTR) develop an exocrinopathy that involves the salivary and lacrimal glands, resembling the pathology of Sjögren's syndrome [85]. It was suggested that human T-cell lymphotropic virus type-1 may represent a primary event in the development of exocrinopathy by virally induced proliferation and perturbation of the function of ductal epithelium. Sialadenitis and inflammation in lachrymal glands histologically resembling Sjögren's syndrome have also been found in mice transgenic for hepatitis C virus envelope genes [86].

Conclusion

Very little is known about the genetics of Sjögren's syndrome. Although not conclusive, however, recent findings in animal breeding studies are promising with respect to resolving issues in Sjögren's syndrome. Of special interest were the major susceptibility loci for autoimmune sialadenitis demonstrated on chromosomes 1, 4 and 10 in murine models. For instance, the chromosomal regions around *Nss1* on chromosome 4 harbour a set of genes that are probably of importance for different kinds of autoimmune syndromes, because several loci associated with autoimmune disease models for systemic lupus erythematosus and autoimmune haemolytic anaemia are clustered around *Nss1* (for review [78]). Interestingly, no association between sialadenitis in the NOD.Q and collagen-induced arthritis was observed [78].

Human linkage studies of Sjögren's syndrome families, in addition to analyses of gene expression signatures on microarrays, will probably be an important source of information in the future. Identification of new genetic markers may lead to development of better diagnostic and prognostic tests in Sjögren's syndrome, including its systemic complications. However, as with the other rheumatic diseases, it is anticipated that both overlap and discrepancies will be detected during genome screens. Given the likely heterogeneity of Sjögren's syndrome, advances will probably not be made without future global collaboration.

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