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Review article

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Genetics and epigenetics of primary Sjögren syndrome: implications for future therapies

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Abstract

In primary Sjögren syndrome (pSS), chronic inflammation of exocrine glands results in tissue destruction and sicca symptoms, primarily of the mouth and eyes. Fatigue, arthralgia and myalgia are also common symptoms, whereas extraglandular manifestations that involve the respiratory, nervous and vascular systems occur in a subset of patients. The disease predominantly affects women, with an estimated female to male ratio of 14 to 1. The aetiology of pSS, however, remains incompletely understood, and effective treatment is lacking. Large-scale genetic and epigenetic investigations have revealed associations between pSS and genes in both innate and adaptive immune pathways. The genetic variants mediate context-dependent effects, and both sex and environmental factors can influence the outcome. As such, genetic and epigenetic studies can provide insight into the dysregulated molecular mechanisms, which in turn might reveal new therapeutic possibilities. This Review discusses the genetic and epigenetic features that have been robustly connected with pSS, putting them into the context of cellular function, carrier sex and environmental challenges. In all, the observations point to several novel opportunities for early detection, treatment development and the pathway towards personalized medicine.

Sections

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Key points

- Advances in the past few years provide new insight into the genetic and epigenetic basis of primary Sjögren syndrome (pSS), and how environmental factors and carrier sex might interact with risk-associated loci.
- Immunomodulatory treatments that affect disease progression and activity have not been identified for pSS and remain unmet clinical needs.
- Data from genetic and epigenetic studies point to Toll-like receptor and interferon signalling, lymphocyte regulation, antigen presentation and target tissue maintenance as the most relevant processes for therapeutic targeting.
- Of the implicated pathogenic processes, Toll-like receptor and interferon signalling, as well as lymphocyte regulation, contain targets of various treatments in development or in clinical trials.
- Novel treatment approaches for pSS could include modification of epigenetic signatures, interference with antigen presentation pathways and antigen-specific immunotherapy.

Introduction

Primary Sjögren syndrome (pSS) is a common autoimmune disease that predominantly affects women[1]. The disease is characterized by inflammation and tissue destruction of the salivary and lacrimal glands, resulting in oral and ocular dryness (denoted as sicca symptoms). Fatigue and arthralgia affect most patients, but presentation of the condition is heterogeneous, and extraglandular manifestations such as synovitis, cutaneous vasculitis, polyneuropathy, interstitial lung disease and tubulointerstitial nephritis develop in 30–40% of patients[2,3] (Fig. 1). For a diagnosis of pSS, current internationally accepted classification criteria require objective measures of decreased production of tears or saliva, as well as immunological aberrances verified either through detection of anti-SSA/Ro autoantibodies, or through histological findings of focal lymphocytic sialadenitis in labial salivary glands[4]. Patient-reported symptom onset often precedes diagnosis by many years, which might relate to an insidious onset of pSS and the fact that sicca symptoms are common in the general population[5]. Therefore, facilitating early diagnosis and identification of disease-modifying treatments that can rescue organ function are central objectives in current research on pSS.

Comorbidities are important contributors to morbidity and mortality in rheumatic disease, and in pSS include an increased risk of cardiovascular disease, especially in patients with autoantibodies[6,7], and a much-increased incidence of lymphoma, with a lifetime risk of around 5%[8,9]. Moreover, in pregnant women, anti-SSA/Ro and anti-SSB/La autoantibodies transfer across the placenta and might cause neonatal lupus with a congenital atrioventricular block in the developing child[10]. Current treatment recommendations for pSS focus on the management of sicca symptoms and stimulation of residual glandular function with muscarinic agonists, but also suggest the use of various conventional synthetic DMARDs (such as hydroxychloroquine) and biologics (such as rituximab) for the treatment of specific organ manifestations[11]. Drugs with an effect on disease progression have not been successfully identified[12], which relates both to the disease heterogeneity and challenges in adequately assessing disease activity in pSS.

pSS is thought to develop when individuals with genetic susceptibility traits are exposed to disease-triggering environmental risk factors, leading to activation of both innate and adaptive immunity. Important factors in pSS immune pathology include augmented activity of the interferon system and B cell hyperactivity, resulting in hypergammaglobulinaemia, disturbed B cell subpopulation frequencies and the production of autoantibodies[13,14]. Further, T cells and B cells infiltrate the affected glands, and can form autoantibody-producing ectopic germinal centres[15,16]. A more precise understanding of the underlying genetics, epigenetics and environmental risk factors is imperative to enable more timely diagnosis and treatment to rescue organ function and improve prognosis.

In this Review, we provide an overview of advances in the understanding of genetic and epigenetic factors in pSS, focusing on well-substantiated observations with genome-wide significance. We discuss how factors such as sex and environment might interact with genetics and influence epigenetic regulation and disease susceptibility and outline how such knowledge points towards specific dysregulated molecular mechanisms, which in turn can instruct the development of highly needed novel treatments.

Genetic studies in pSS

Genetics refers to the study of DNA sequences and variation therein such as single nucleotide polymorphisms (SNPs) or mutations. Most of the genetic factors associated with complex diseases are common single nucleotide variants (often defined as >1% carriers) in non-coding segments of our DNA, posing a challenge for understanding how genetic features translate into pathogenic mechanisms. Furthermore, concordance rates of autoimmune diagnoses in monozygotic twins are typically below 30%[17,18], providing evidence that non-genetic factors are also of major importance in these diseases. Such extrinsic and intrinsic factors can, however, interact with genetic features[19], and modulation of the epigenome represents one way in which these interactions can translate into phenotypic outcomes. Important approaches for achieving a better understanding of the underlying genetics of complex diseases include case–control association studies and the less commonly performed family linkage studies. Association studies typically either focus on a specific genetic region in candidate gene studies or use an unbiased approach through large-scale or genome-wide association studies (GWAS).

Several lines of evidence confirm the role of genetic predisposition in the development of pSS. For example, compared with the general population, the occurrence of pSS is higher among siblings of patients with pSS, the familial incidence of other autoimmune conditions is also higher[20] and a few existing reports indicate increased co-occurrence of pSS in twins[21–24], although estimates of twin concordance rates are still lacking. Knowledge on the genetics of pSS is building, but the number of publications from genetic studies remains low compared with other autoimmune diseases (such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and multiple sclerosis) (Fig. 2). Studies in pSS have identified associations in the HLA locus as well as in >20 non-HLA loci that reach genome-wide significance ($P < 5 \times 10^{-8}$) (Table 1). Associations that do not reach genome-wide significance might also be of interest to explore, as reviewed elsewhere[25,26], although data should be interpreted with care. In this Review, we focus on those associations with genetic regions that reach genome-wide significance.

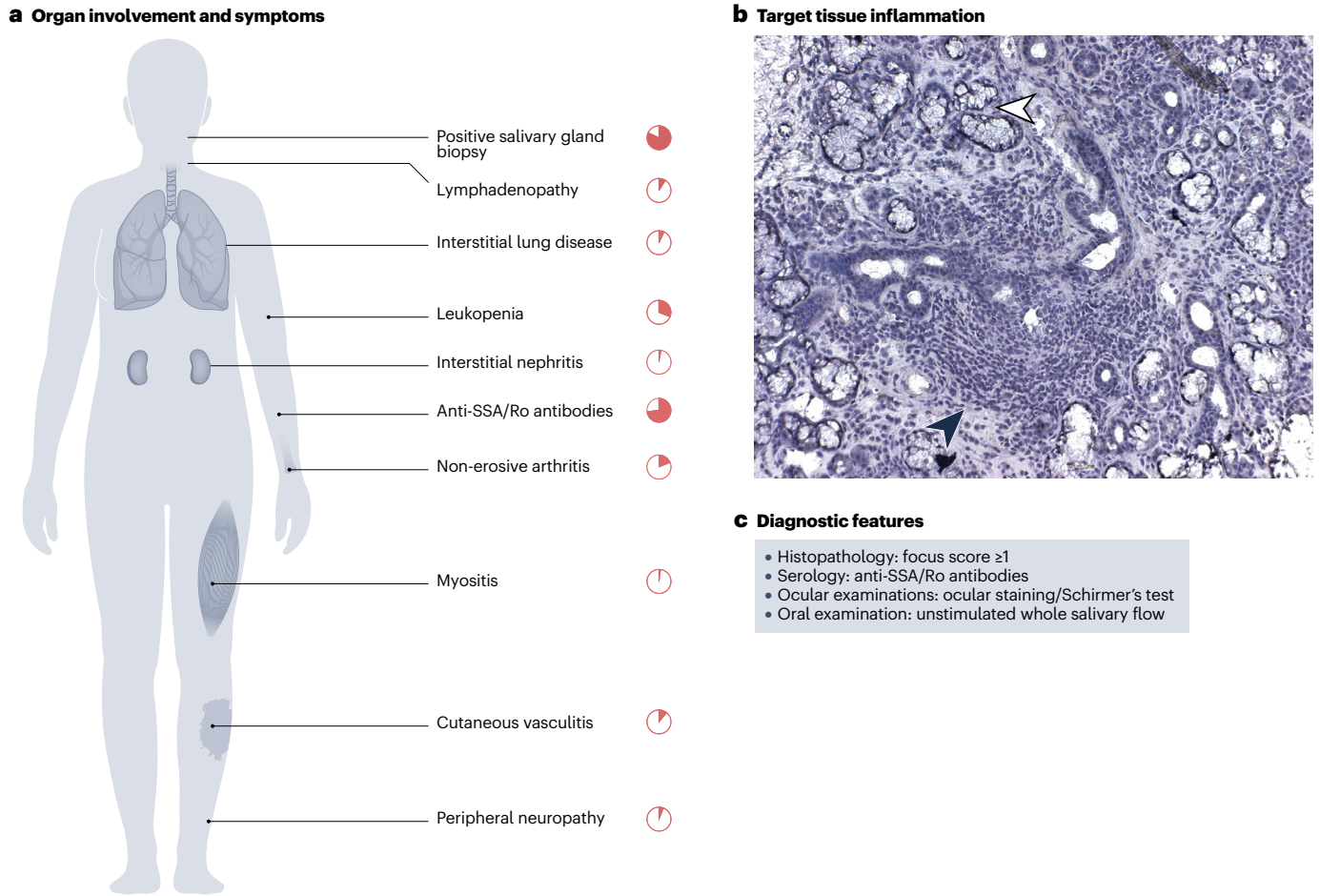


Fig. 1 | Clinical features of Sjögren syndrome. The clinical presentation of primary Sjögren syndrome (pSS) is heterogeneous, and patients can present with various symptoms and organ involvement. **a**, Lymphocyte infiltration and tissue destruction of the salivary glands, as well as the presence of anti-SSA/Ro autoantibodies are hallmarks of the disease, but other features such as leukopenia and non-erosive arthritis are relatively common. The frequency of the best-described organ manifestations in patients with pSS are represented[3,32]. **b**, Lymphocytic infiltrate in a haematoxylin-stained minor salivary gland biopsy section analysed as part of the diagnostic procedure for Sjögren syndrome. The infiltrate (filled black arrowhead) surrounds dilated secretory ducts and penetrates into glandular tissue. Some remaining acini are indicated by a white arrowhead. **c**, Diagnostic features required for classification as Sjögren syndrome include histological findings of at least one focus of lymphocytic sialadenitis in a 4 mm^2 labial salivary gland biopsy (focus score >1), the presence of anti-SSA/Ro autoantibodies and objective measures of decreased production of tears (ocular staining score or Schirmer's test) or saliva (unstimulated whole salivary flow rate).

The discovery of pSS-associated loci

In pSS, four GWAS[27–30], one large-scale study employing the ImmunoChip (a custom SNP array) and other large-scale arrays[31], a targeted sequencing study[32] and five candidate gene studies[33–37] have identified various loci of genome-wide significance in either European populations, Asian populations or both (Fig. 2).

More than a decade ago in 2012, the first association at genome-wide significance was reported in a candidate gene study of the HLA class III locus by Bolstad et al.[37]. The study identified an association between a SNP in the promoter region of *TNF* and pSS; however, given the high linkage disequilibrium of the whole HLA region, whether this observation represents an independent signal is unclear. In 2013, Lessard et al.[31] studied patients of European ancestry using several different large-scale arrays and reported genome-wide significant associations in six non-HLA loci (*IRF5–TNPO3*, *STAT4*, *IL12A*, *FAM167A–BLK*, *CXCR5* and *TNIP1*), as well as confirming previously reported HLA associations. Results from a GWAS performed by Li et al.[27] in a Han Chinese population were published in the same issue of *Nature Genetics*. The study established associations between pSS and *GTF2IRD1–GTF2I* and *TNFAIP3* (although the association with *TNFAIP3* had already been indicated in a previous candidate gene study[38]) and confirmed the association of *STAT4* and the HLA region with pSS in Han Chinese patients. The *GTF2IRD1–GTF2I* association was later confirmed by Song et al.[28] in a 2016 GWAS of Han Chinese female patients, and further characterized by Zhao et al.[34], who identified a missense variant in *NCF1* located 62 kb from the associated SNP rs117026326.

In 2017, Taylor et al.[29] analysed patients of both European and Asian ancestry, as part of the Sjögren's International Collaborative Clinical Alliance (SICCA) initiative, and revealed pronounced ancestry-specific differences in genetic associations with pSS, including in

the HLA locus, while confirming associations at *IRF5* and *STAT4*. In cohorts of patients from France and the UK, another 2017 study by Carapito et al.[33] reported an association between pSS and an allele of the non-conventional MHC-encoded class I gene (*MICA*). The association was later confirmed as being independent of pSS-associated MHC class II signals[32].

In an alternative approach that involved *cis*-expression quantitative trait locus (eQTL) analyses of type I interferon-inducible transcripts (Supplementary Box 1), Li et al.[35] found multiple associations between pSS and a SNP in *OAS1* that resulted in shifted splicing of the gene, and in a following candidate gene investigation, a meta-analysis of cohorts of patients of European ancestry identified *OAS1* as a susceptibility locus. Also employing a candidate gene approach, Qu et al.[36] identified a genome-wide significant association with *IKZF1* in a Han Chinese population. Using targeted sequencing, Thorlacius et al.[32] confirmed and refined the signal from the HLA locus, revealing three independent signals in patients with pSS and anti-SSA/Ro and/or anti-SSB/La autoantibodies. This study also observed the highest odds ratio so far at 6.1 for a genetic association with anti-SSA/Ro autoantibody- and/or anti-SSB/La autoantibody-positive pSS (Fig. 3).

Most recently, a GWAS in patients of European ancestry by Khatri et al.[30] identified seven novel loci (*NAB1*, *PTTG1–MIR146A*, *XKR6*, *MAPT–CRHR1*, *RPTOR–CHMP6–BAIAP2*, *TYK2* and *SYNGR1*), and a meta-analysis performed with additional ImmunoChip-derived data revealed three additional loci (*CD247*, *PRDM1–ATG5* and *TNFAIP3*) that are associated with pSS at genome-wide significance. In this study, polygenic risk scores for pSS were calculated for the first time, reaching similar predictive values to those that had previously been indicated for SLE and RA[30].

Associations with subphenotypes and comorbidities of pSS

pSS is a heterogeneous condition with several subphenotypes, and it is often accompanied by comorbidities, both features of which are probably dependent on discrete genetic variations. Several genetic associations of genome-wide significance are specific to patients positive for anti-SSA/Ro and/or anti-SSB/La autoantibodies[32]. This group of patients are more prone to systemic disease with extraglandular manifestations than other patients with pSS[32], and although it has not yet been demonstrated at a genome-wide significant level, it is possible that genetic variants associated with anti-SSA/Ro and/or anti-SSB/La

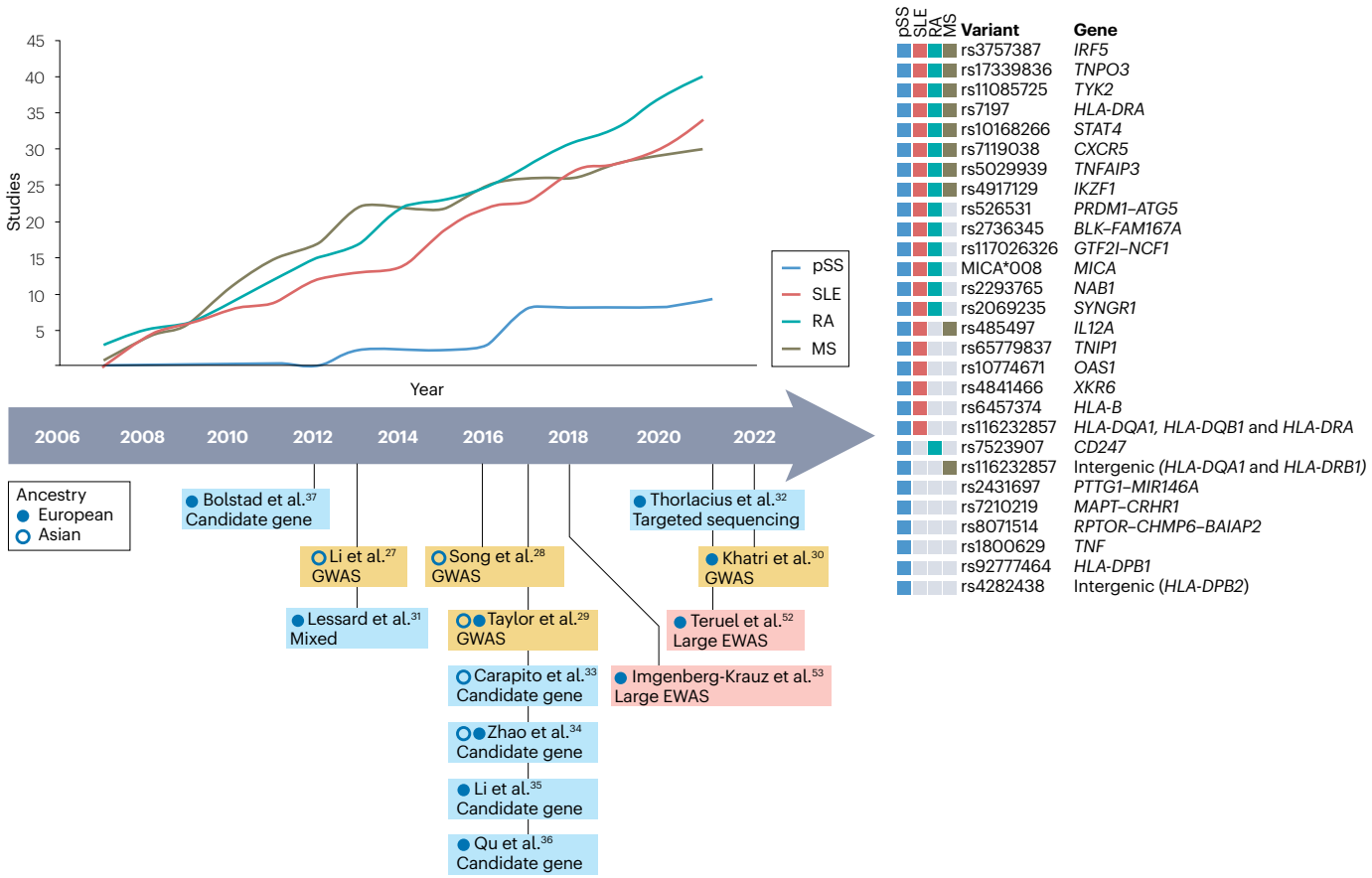


Fig. 2 | Studies identifying genetic risk loci of genome-wide significance. An increasing number of studies on primary Sjögren syndrome (pSS) and selected other autoimmune diseases are registered in the genome-wide association studies (GWAS) catalogue[205]. However, the number of studies that have identified genetic variants of genome-wide significance in pSS is still low compared with other autoimmune diseases. In the timeline, key papers in pSS that identify novel genetic loci at genome-wide significance are indicated, as well as large-scale epigenome-wide association studies (EWAS) that included ≥100 patients with pSS. Some genetic risk loci identified for pSS are also associated with other autoimmune disease. Many of the non-HLA variants associated with pSS are also associated with systemic lupus erythematosus (SLE), whereas fewer variants overlap with rheumatoid arthritis (RA) or multiple sclerosis (MS). Some variants seem to specifically increase the risk of pSS[30,205].

Table 1 | Genetic loci associated with primary Sjögren syndrome

Variant	Position (Chr:bp)	Gene	Function	Odds ratio	*P* value	Ref.
rs7523907	1:167427247	*CD247*	T cell receptor signalling	0.85	9.33×10^{-9} [a]	30
rs10168266	2:191071078	*STAT4*	Intracellular signalling	1.44	2×10^{-17}	27
rs2293765	2:191520845	*NAB1*	Transcriptional repression	1.24	5.53×10^{-14}	30
rs485497	3:160001345	*IL12A*	The 35-kDa subunit of IL-12	1.3	1×10^{-10}	31
rs6579837	5:151055333	*TNIP1*	Inhibits NF-κB activation	1.43	3×10^{-8}	31
rs2431697	5:159879978	*PTTG1*	Anaphase-promoting complex substrate	0.83	3.33×10^{-9}	30
		MIR146A	Post-transcriptional regulation of gene expression			
rs6457374	6:31272261	*HLA-B*	Presents peptides derived from the endoplasmic reticulum lumen	3.27	3.52×10^{-27}	33
rs2523607	6:31322790	*HLA-B*	Presents peptides derived from the endoplasmic reticulum lumen	5.27	5.30×10^{-58}	32
MICA*008	6:31371356	*MICA*	Stress-induced ligand for the natural killer cell-activating protein NKG2D	2.24	2.61×10^{-35}	33
rs1800629	6:31543031	*TNF*	Multifunctional pro-inflammatory cytokine	2	2.48×10^{-10}	37
rs7197	6:32412580	*HLA-DRA*	Presents peptides derived from extracellular proteins	1.56	2.6×10^{-25}	32
rs116232857	6:32597064	Intergenic (*HLA-DQA1* and *HLA-DRB1*)	Presents peptides derived from extracellular proteins	2.42	1.14×10^{-67}	31
			Presents peptides derived from extracellular proteins			
rs115575857	6:32659645	*HLA-DQA1*	Presents peptides derived from extracellular proteins	3.65	3.7×10^{-90}	31
		HLA-DQB1				
		HLA-DRA				
rs9277464	6:33053352	*HLA-DPB1*	Presents peptides derived from extracellular proteins	1.65	3×10^{-7}	29
rs4282438	6:33072172	Intergenic (*HLA-DPB2*)	Presents peptides derived from extracellular proteins	1.58	8.77×10^{-25}	27
rs5029939	6:137874586	*TNFAIP3*	Inhibits NF-κB activation	1.67	8×10^{-9}	27
rs526531	6:138243700	*PRDM1*	Repressor of IFNβ expression	1.13	4.86×10^{-8} [a]	30
		ATG5	Involved in autophagic vesicle formation			
rs4917129	7:50323074	*IKZF1*	Transcription factor that regulates lymphocyte differentiation	0.7	4.24×10^{-8}	36
rs117026326	7:74711703	*GTF2I*	Phosphoprotein with roles in transcription and signal transduction	2.2	1×10^{-53}	27
		NCF1	Subunit of neutrophil enzyme NADPH oxidase			
rs3757387	7:128936032	*IRF5*	Transcription factor with diverse roles	1.44	3×10^{-19}	31
rs17339836	7:129041008	*TNPO3*	Nuclear import receptor	1.58	2×10^{-16}	31
rs4841466	8:10829159	*XKR6*	Unknown	1.17	3.77×10^{-8}	30
rs2736345	8:11494976	*BLK*	Tyrosine kinase involved in B cell development	1.3	5×10^{-10}	31
		FAM167A	Unknown			
rs7119038	11:118867572	*CXCR5*	Receptor for the chemokine CXCL13	1.35	1×10^{-8}	31
rs10774671	12:113356943	*OAS1*	Interferon-induced antiviral enzyme	0.75	2.59×10^{-9}	35
rs8071514	17:10462513	*RPTOR*	Controls mTORC1 activity involved in cell growth and survival	0.84	1.64×10^{-8}	30
		CHMP6	Probably involved in the biosynthesis of endosomes			
		BAIAP2	Adapter protein that links membrane-bound small G proteins to cytoplasmic effector proteins.			
rs7210219	17:78964083	*MAPT*	Promotes microtubule assembly and stability	0.78	2.4×10^{-10}	30
		CRHR1	A receptor that binds to corticotropin-releasing hormones			
rs11085725	19:39747780	*TYK2*	Involved in interferon and cytokine signalling	0.78	7.17×10^{-13}	30
rs2069235	22:39747530	*SYNGR1*	Unknown	1.21	5.06×10^{-10}	30

bp, base pair; Chr, chromosome; mTORC1, mechanistic target of rapamycin complex 1; NF-κB, nuclear factor-κB. [a]*P* value from a meta-analysis combining more than one study or cohort.

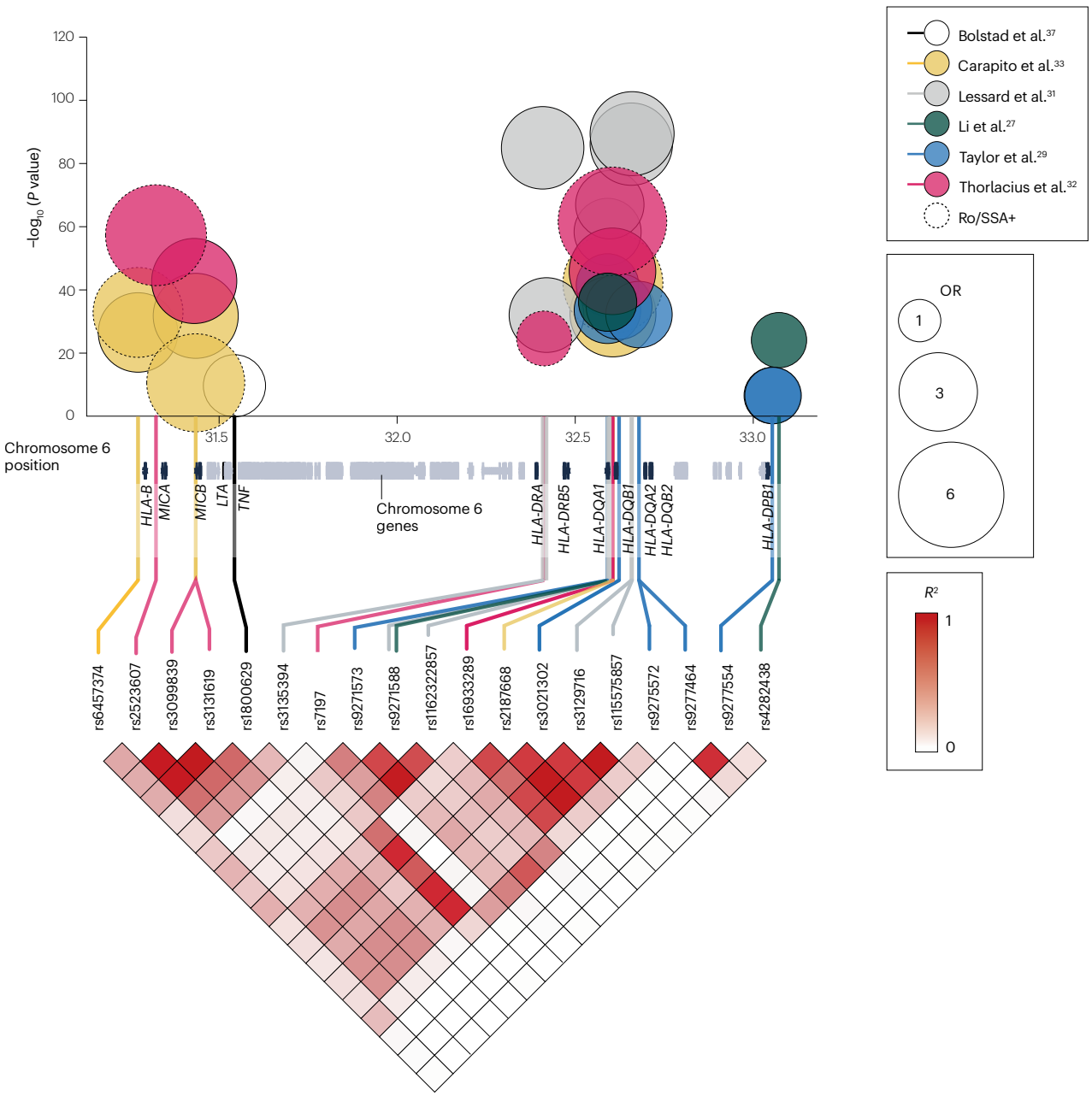


Fig. 3 | Associations between variants within the HLA locus and primary Sjögren syndrome. A large number of variants that are associated with primary Sjögren syndrome (pSS) are located within the HLA locus on chromosome 6. The graph depicts chromosome position (*x* axis), odds ratio (OR; bubble size) and significance level (*y* axis) of these disease-associated genetic variants, which are coloured by study. Dotted lines indicate data generated from cohorts that included only patients with pSS who are positive for anti-SSA/Ro and/or anti-SSB/La autoantibodies. Linkage disequilibrium (expressed in terms of the squared correlation (R^2)) between the depicted variants in Utah residents of northern and western European ancestry (a population of the 1000 Genomes Project, Code CEU) is indicated in the bottom triangle (data taken from LDlink[206]). Genes near the associated variants are annotated (using data from the UCSC Genome Browser on Human (GRCh37/hg19)[207]).

autoantibodies associate with discrete systemic engagement or comorbidities in pSS.

Studies of genetic variations in relation to other pSS-related features such as specific symptoms or comorbidities are few, but in 2021, a meta-analysis of patients with pSS from Norwegian and Swedish cohorts identified a genome-wide significant association between variants in the *RTP4–MASP1* locus and fatigue in patients with pSS[39]. No genome-wide significant associations have yet been identified for the pSS-associated comorbidity lymphoma, but several studies imply a role for variants in *TNFAIP3* in this comorbidity[40–42]. This gene, together

with other genetic loci implicated in lymphoma development in pSS but for which the reported associations do not reach genome-wide significance, have been reviewed elsewhere[43,44].

Epigenetic studies in pSS

Epigenetics refers to processes that influence gene expression without affecting the actual DNA sequence. These processes include histone modifications, non-coding RNA activity and DNA methylation, the last of which is the most thoroughly studied epigenetic mechanism in pSS. The addition of methyl (CH_3) groups at cytosine guanine dinucleotide (CpG) sites in gene promoter regions (hypermethylation) generally results in repression of gene expression[45]. Conversely, hypomethylation of DNA is associated with augmented gene expression levels[45].

In keeping with this association, many of the genes identified as hypomethylated or hypermethylated in studies of pSS are differentially expressed at the mRNA level (Table 2).

Researchers initially discovered that type I interferon-regulated genes were expressed at high levels in the blood[46,47] and salivary glands[48,49] of patients with pSS and later found DNA hypomethylation at these genes. Methylation levels are influenced by environmental factors, including drugs, and different cells and tissues have distinct methylation patterns (known as methylomes), which are linked to cell-specific activation of particular signalling pathways and transcription

Table 2 | Top sites identified as differentially methylated in primary Sjögren syndrome

CpG site	Position (Chr:bp)	Gene	*P* value	Methylation status (hypermethylated (+) or hypomethylated (−))	Tissue	Interferon induced?[a]	Refs.
cg07515989	1:43250763	NA	1.39×10^{-8}	+	Salivary glands	NA	53
cg03607951	1:79085586	*IFI44L*	9.9×10^{-67}	−	Blood and B cells	Yes	52,53
cg04268125	1:154579384	*ADAR*	1.83×10^{-11}	−	Blood	Yes	52
cg10549986	2:7018153	*RSAD2*	1.4×10^{-17}	−	B cells	Yes	53
cg09858955	2:58135951	*VRK2*	2.14×10^{-14}	−	Blood	Yes	52
cg22930808	3:122281881	*PARP9–DTX3L*	2.4×10^{-55}	−	Blood and B cells	Yes	52,53
cg06981309	3:146260954	*PLSCR1*	4.1×10^{-51}	−	Blood and B cells	Yes	52,53
cg24678928	4:169240829	*DDX60*	2.84×10^{-16}	−	Blood	Yes	52
cg17608381	6:29911550	*HLA-A*	3.4×10^{-15}	−	Blood	Yes	53
cg24399349	7:55517045	NA	2.38×10^{-8}	+	Salivary glands	NA	53
cg02680398	8:4629524	*CSMD1*	1.22×10^{-8}	−	Salivary glands	No	53
cg01232121	8:58177661	*LOC286177*	1.59×10^{-8}	−	Salivary glands	No	53
cg14864167	8:66751182	*PDE7A*	2.55×10^{-10}	−	Blood	Yes	52
cg06188083	10:91093005	*IFIT3*	8.85×10^{-18}	−	Blood	Yes	52
cg05552874	10:91153143	*IFIT1*	2.7×10^{-56}	−	Blood and B cells	Yes	52,53
cg06999856	10:135260170	NA	2.79×10^{-8}	+	Salivary glands	NA	53
cg23570810	11:315102	*IFITM1*	6.1×10^{-38}	−	Blood and B cells	Yes	52,53
cg23198815	11:87184120	NA	3.73×10^{-8}	−	Salivary glands	NA	53
cg14943355	12:3980704	*PARP11*	2.85×10^{-16}	−	Blood	Yes	52
cg04740359	12:5603542	*NTF3*	1.39×10^{-9}	−	Salivary glands	Yes	53
cg20870559	12:113416518	*OAS2*	1.02×10^{-9}	−	Salivary glands	Yes	53
cg12439472	13:43565399	*EPSTI1*	2.32×10^{-17}	−	Blood	Yes	52
cg18329187	14:103989711	*CKB*	2.8×10^{-8}	+	Salivary glands	Yes	53
cg03425812	15:45005363	*B2M*	6.11×10^{-11}	−	Blood	Yes	52
cg07839457	16:57023022	*NLRC5*	7.59×10^{-20}	−	Blood	Yes	52
cg25330422	17:40467382	*STAT3*	3.2×10^{-13}	+	B cells	Yes	53
cg00871371	17:75371476	*SEPTIN9*	3.15×10^{-8}	+	Salivary glands	No	53
cg16638092	17:78800774	*RPTOR*	1.72×10^{-8}	+	Salivary glands	No	53
cg05825244	20:2730488	*EBF4*	2.4×10^{-11}	+	Blood	No	53
cg22862003	21:42797588	*MX1*	7.9×10^{-63}	−	Blood and B cells	Yes	52,53
cg14293575	22:18635460	*USP18*	9.7×10^{-14}	−	B cells	Yes	53

bp, base pair; Chr, chromosome; CpG, cytosine guanine dinucleotide; NA, not available. [a]Defined as absolute fold change of 2.0 in the interferome database[204].

factors[50]. Initial studies in pSS, which will not be reviewed here, assessed global DNA methylation levels and specific CpG sites in candidate genes[51]. Since 2014, the involvement of DNA methylation has been studied in several epigenome-wide association studies (EWAS)[52–59] to identify genetic regions where methylation levels differ between patients with pSS and healthy individuals.

Two large-scale EWAS that each included ≥100 patients have been performed[52,53], and the top associated loci are listed in Table 2. In one of the EWAS, Teruel et al.[52] assessed differentially methylated positions and regions in whole blood from 189 patients with pSS and 220 healthy individuals. The most robustly associated differentially methylated positions and regions were located within type I interferon-regulated genes, but differentially methylated positions were also enriched in pathways related to the metabolism of collagen and the organization of the extracellular matrix. Notably, the detected epigenetic signatures were observed only for anti-SSA/Ro antibody-positive patients and were not present in autoantibody-negative patients. Similarly, the other EWAS by Imgenberg-Kreuz et al.[53] found extensive hypomethylation at regulatory enhancer and promoter regions of interferon-regulated genes in whole-blood analysis of 100 patients and 400 healthy individuals, and this signature was more pronounced in autoantibody-positive patients. Subset analyses of $CD19^+$ B cells and minor salivary gland biopsy samples also revealed hypomethylation at interferon-regulated genes, which correlated with increased gene expression levels in B cells. In whole blood, the most prominent finding in both of these large-scale studies was hypomethylation at the type I interferon-regulated gene *IFI44L*.

Several smaller EWAS have also assessed epigenome-wide DNA methylation in minor salivary gland biopsy samples[53,56,59], $CD4^+$ T cells[54,55], $CD19^+$ B cells[53,55] and/or cultured minor salivary gland epithelial cells[57] from patients with pSS. Altogether, the findings suggest that differential DNA methylation is more pronounced in B cells than in T cells[55], and most studies detect prominent hypomethylation at interferon-regulated genes. A 2021 study of minor salivary gland biopsy samples, which included 64 patients with pSS and 67 individuals with sicca symptoms but not pSS, found that close to half of the detected differentially methylated regions were located in the HLA locus, with corresponding methylation quantitative trait loci (meQTLs) in the regions encompassing the *HLA-DQA1*, *HLA-DQB1* and *HLA-DQA2* loci[59]. Conversely, relatively few non-HLA loci genetically associated with pSS have been identified as differentially methylated in EWAS.

Implicated pathogenic processes

Important features of pSS immunopathogenesis include augmented B cell activity, crosstalk between B cells and T cells and the resulting formation of ectopic lymphoid tissue, disruption of salivary gland tissue associated with increased apoptosis and exposure of autoantigens, persistently elevated levels of pro-inflammatory cytokines and high expression of type I interferon-regulated genes[13,60]. Interestingly, most of the identified genetic variants and epigenetic signals associated with pSS can be assigned to genes involved in these processes, including Toll-like receptor (TLR) and interferon pathways, lymphocyte regulation, antigen presentation and target tissue maintenance (Fig. 4), as discussed in the next section.

TLR signalling and interferon pathways

The type I and type II interferon systems are highly activated in the peripheral blood and target tissue of most patients with pSS[47,48,61,62]. This feature of increased type I and type II interferon activity is also evident in DNA methylation studies, in which interferon-regulated genes are hypomethylated and the expression of the corresponding genes is increased in pSS[52,53]. Activity of the type I interferon system can be assessed by measuring hypomethylation at type I interferon-regulated genes[63], a method that has been employed to define patient subsets in pSS[64]. Beyond DNA methylation studies, several disease-associated loci of genome-wide significance encode genes related to type I and/or type II interferon signalling, including *IRF5*, *STAT4*, *TYK2*, *IL12A* and *OAS1* (Fig. 4).

The expression of the transcription factor interferon regulatory factor 5 (IRF5) is induced by TLR and type I interferon signalling, and IRF5 in turn regulates the expression of type I interferon and other pro-inflammatory cytokines[65]. The genetic association of *IRF5* with disease has been replicated across ancestries in pSS, and also in several other autoimmune diseases (Fig. 2). Interestingly, variants in *IRF5* and *STAT4* have additive effects on the risk of pSS[66]. *STAT4* encodes a transcription factor that functions downstream of IL-12 and type I interferon receptors, thus functionally connecting this gene to other pSS-associated loci. *STAT1* is a neighbour of *STAT4* on chromosome 2, and the mRNA levels of *STAT1* differ considerably depending on the risk variants in the *STAT1–STAT4* locus in B cell lines[67] and monocyte-derived macrophages[68], implicating signal transducer and activator of transcription 1 (STAT1) in systemic autoimmune diseases. However, the *STAT4* risk allele rs7574865[T] is not associated with differential protein levels of STAT1 or STAT4 in resting peripheral blood mononuclear cells from patients with SLE[69]. Also, no eQTLs were identified for risk variants in the *STAT1–STAT4* locus in peripheral blood from patients with pSS and healthy individuals[31]. However, as STAT1 is directly implicated in pSS pathology, the effect of genetic variants in this region on STAT1 expression and function requires further investigation.

The tyrosine kinase TYK2 transmits signals downstream of multiple cytokine receptors, including the type I interferon and IL-12 receptors, and is therefore central in both interferon signalling and lymphocyte activation[70]. Genetic variants in *TYK2* associated with pSS are protective, possibly owing to a reduction in signalling downstream of pro-inflammatory cytokine receptors[71]. *IL12A* encodes the p35 subunit of IL-12, which signals through the Janus kinase (JAK)–STAT pathway (including TYK2 and STAT4) and has several functions but is especially important for the differentiation of naive T cells into T helper type 1 (T_H1) cells[72]. Activation of the IL-12 receptor leads to the production of interferon-γ (IFNγ) by T cells and natural killer cells[73]. Finally, *OAS1*, as a type I interferon-induced gene, has an important role in antiviral responses. The pSS-associated SNP rs10774671 in *OAS1* results in alternative splicing of the gene and generates an isoform of 2′–5′-oligoadenylate synthase 1 (OAS1) with a reduced function[35]; in addition to being connected with pSS, this SNP is also associated with increased risk of severe coronavirus disease 2019 (COVID-19)[74], as well as susceptibility to West Nile virus and hepatitis C virus infection[75,76].

Regarding the most recently discovered associations, variants in *NAB1* have previously been associated with seropositive systemic autoimmunity in a GWAS meta-analysis of systemic sclerosis, SLE, RA and idiopathic inflammatory myopathies[77]. The encoded protein NGFI-A binding protein 1 (NAB1) functions as a transcriptional repressor[78], and, in mice, downregulates the expression of *Ifngr1* (ref. [79]). Interestingly, a variant in *TNFAIP3* is an eQTL for *IFNGR1* in the salivary gland, further tying type II interferon responses to potential pathogenic processes[30]. The microRNA (miRNA) encoded by *MIR146A* regulates inflammation through a negative feedback loop downstream of TLR and cytokine receptors[80,81], and genetic variation in this gene is associated with numerous inflammatory diseases[82]. High expression of miR-146a has

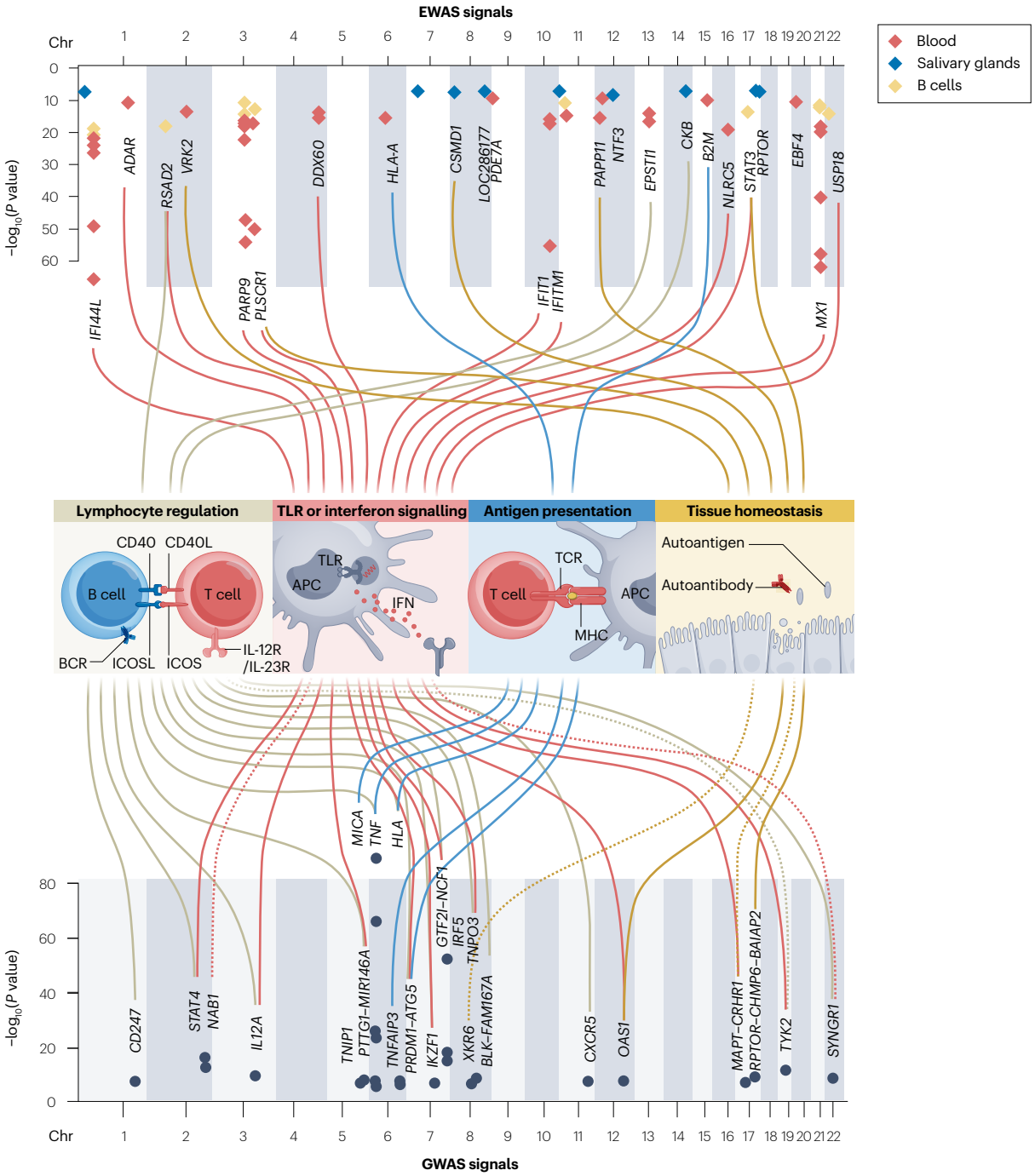


Fig. 4 | Pathogenic processes implicated by genetic and epigenetic studies. Genetic and epigenetic studies implicate various genes in the development of primary Sjögren syndrome (pSS). Most of these genes have functions in lymphocyte regulation, Toll-like receptor (TLR) or interferon (IFN) signalling, antigen presentation and tissue homeostasis, pointing to a role for these processes in the pathogenesis of pSS. The position and significance level of methylation signals associated with pSS for various tissues are shown in the upper Manhattan plot, including associations found in blood (red dots), salivary glands (blue dots) and B cells (yellow dots). Genetic variants associated with pSS at genome-wide significance and their annotated genes are shown in the lower Manhattan plot. The genes are linked by coloured cords to the four main pathogenic processes, according to gene function; solid lines indicate a direct function, whereas dotted lines indicate an indirect connection to these processes. Data taken from the studies listed in Tables 1 and 2. APC, antigen-presenting cell; BCR, B cell receptor; Chr, chromosome; EWAS, epigenome-wide association studies; GWAS, genome-wide association studies; ICOS, inducible T cell co-stimulator; ICOSL, inducible T cell co-stimulator ligand; TCR, T cell receptor.

been reported in peripheral blood mononuclear cells from patients with pSS[83–87], primarily in CD4$^+$ T cells[88].

Lymphocyte regulation

Features of B cell hyperactivity in pSS include hypergammaglobulinaemia, high levels of B cell-activating factor (BAFF), disturbances in B cell subset proportions with high relative numbers of naive B cells and low frequencies of CD27$^+$ memory B cells[89], and the development of B cell lymphomas[8]. T cells are present at sites of autoimmune inflammation and stimulate the autoreactive B cells[90]. In keeping with these processes, many genetic regions associated with pSS contain genes involved in the regulation of lymphocytes[30].

Disease-associated variants in the *FAM167A–BLK* locus were first described in a candidate gene study in Swedish and Norwegian patients[91]. A later study described a prominent disease-associated variant in the shared promoter region of the two genes, which are transcribed in opposite directions, along with notable eQTLs for both genes[31]. *BLK* encodes the Src family tyrosine kinase BLK, which is an important signalling molecule downstream of the B cell receptor, whereas *FAM167A* encodes the protein FAM167A (also known as DIORA1), which is highly expressed in B cells and in the lung[92,93]. Variants near *CXCR5* implicate the importance of the CXCR5–CXCL13 axis in pSS immunopathology, a signalling pathway that is crucially involved in the migration of B cells and T cells as well as the formation of germinal centres[94]. A risk variant in this locus is an eQTL for *CXCR5* in CD19$^+$ B cells[94]. Notably, mice lacking *Cxcr5* fail to develop several types of peripheral lymph node and form few and abnormal Peyer's patches[95]. Furthermore, dysregulation of the CXCR5–CXCL13 axis is amply documented in pSS[96]. *DDX6* is a neighbour of *CXCR5* and a SNP in the promoter/enhancer region of *DDX6* and *CXCR5* is an eQTL of *DDX6* in T cells[97], which is of interest not least because DDX6 is implicated in the suppression of interferon-stimulated genes[98].

Other pSS-associated loci also contain several genes involved in lymphocyte regulation. For instance, *CD247* encodes the T cell receptor-ζ, which is part of the T cell receptor–CD3 complex and is thus important for signal transduction upon antigen stimulation. Notably, *CD247* is hypomethylated in CD4$^+$ T cells in pSS[54], further supporting the relevance of the association of the *CD247* locus with the disease. Another relevant gene is *PRDM1*, which encodes B lymphocyte-induced maturation protein 1 (BLIMP1), an IRF5-regulated transcription factor crucial for lymphocyte development and the regulation of B cell differentiation[99]. Finally, a pSS-associated region contains *IKZF1*, which encodes a transcription factor that is also involved in lymphocyte differentiation and proliferation and is regulated by various IRFs, including IRF5 (ref. [100]).

Antigen presentation

The HLA locus harbours by far the strongest genetic associations with pSS[30]. This gene-dense region is difficult to dissect owing to high linkage disequilibrium, but disease-associated signals in both the HLA class I and II regions are well established and contain eQTLs that often lead to increased expression of HLA molecules[31] (Supplementary Box 1).

Data from several studies suggest that the HLA associations occur predominantly in patients with anti-SSA/Ro and/or anti-SSB/La autoantibodies, with the most relevant being HLA class II genes in the HLA-DR and HLA-DQ loci[32]. Specifically, *DRB1*03:01*, *DQA1*05:01* and *DQB1*02:01* have the best established associations[101], although researchers have also identified associations with variants in the region containing *HLA-B*, *MICA* and *HCP5* (refs. [32,33]). Emerging data suggest that blood levels of IFNα in pSS are associated with polymorphisms in the HLA-DQ locus, indicating crosstalk between these two pathways[102].

The proteins encoded by the HLA genes present antigens to T cells and have a central role in activation and regulation of the immune system. Notably, a pSS-associated genomic region contains *ATG5*, which encodes a protein required for proper phagocytosis, processing and presentation of peptides on HLA class II[103].

Target tissue maintenance

Ductal cells and salivary gland epithelial cells (SGECs) in affected glands are thought to actively participate in the pathogenesis of pSS through the secretion of chemoattractants and the expression of HLA class I molecules and adhesion molecules[104]. Defective apoptotic mechanisms in SGECs are implicated in pSS[105], and indeed several genes in loci associated with pSS have a role in these processes (Fig. 4).

Interestingly, a disease-associated variant in the *PRDM1–ATG5* locus is an eQTL for *ATG5* in salivary gland tissue[30]. ATG5 is involved in autophagy and apoptosis, among several other immune processes[106] and is expressed at high levels in large and organized salivary gland infiltrates in pSS[107]. Regarding the disease-associated locus *MIR146A–PTTG1*, securin (encoded by *PTTG1*) is a regulatory protein involved in chromosome stability, cell cycle regulation and apoptosis[108]. However, miR-146a (encoded by *MIR146A*) is perhaps the most likely candidate gene to have a functional impact on pSS disease processes, given its properties in modulating immune responses. Within the disease-associated region *RPTOR–CHMP6–BAIAP2*, *RPTOR* encodes a scaffold protein that is a component of the mechanistic target of rapamycin complex 1 (mTORC1), which has an importance for both cell growth and apoptosis[109], but this complex has not yet been studied in pSS. Finally, two disease-associated regions contain *TNFAIP3* and *TNIP1*, encoding A20 and an A20-binding protein, which function to suppress nuclear factor-κB (NF-κB) signalling as well as TNF-induced apoptosis[110]. In addition to pSS, genetic variants in the *TNFAIP3* locus are associated with RA, SLE, multiple sclerosis and inflammatory bowel disease, among other diseases[111]. The expression of *TNFAIP3* is downregulated in B cells in pSS, and a missense polymorphism in the gene is associated with lymphoma development[41].

EWAS have revealed dysregulated methylomes in the minor salivary glands of patients with pSS that probably affect target tissue maintenance[53,56,59]. For example, an analysis of minor salivary gland biopsy samples found that global methylation levels are reduced in pSS and are associated with glandular lymphocyte infiltration and the presence of anti-SSB/La autoantibodies, but are not associated with EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) scores[112]. Furthermore, a separate study found that the expression of DNA methylation mediators (including DNA methyltransferases 1 and 3B) in the minor salivary glands is higher in patients with pSS than in individuals with non-pSS sicca symptoms, which in turn is positively associated with the expression of LINE-1 retroelements[113]; this is of interest as LINE-1 retroelements might function as endogenous triggers of immune activation in the context of interferon-driven autoimmune diseases[114]. Notably, dysregulated methylation levels have also been reported in saliva from patients with pSS[115].

Genes with unknown or other functions

Various pSS susceptibility loci encompass genes with no immediately obvious link to pathways implicated in the disease, either because little is known about the gene function or because the function is difficult to connect with pSS immunopathology. Examples of such genes include *XKR6*, *TNPO3*, *CHMP6*, *MAPT*, *CRHR1*, *SYNGR1* and *BAIAP2* (refs. [30,31]) (Table 1). Further investigation into the function of these genes and a

better understanding of the pathogenic process of pSS should reveal whether the genes are indeed important for disease development.

Interaction of genetic susceptibility with other risk factors

Although tremendous progress has been made in understanding the genetic prerequisites for pSS, disease-associated loci generally convey only a modestly increased risk of pSS, with odds ratios between 1 and 2 (Table 1) when estimated without regard to other intrinsic or extrinsic factors. Thus, genetic factors seem to explain only a limited proportion of pSS development. Studies of other rheumatic diseases show that genetic susceptibility and other risk factors can interact. The contribution of environmental factors in the pathogenesis of pSS is, however, understudied, and replication is needed for the few published findings[19]. In this section, we discuss the available studies and how identified risk factors might interact with genetic traits.

Environmental factors

Environmental risk factors that have been suggested for pSS include infection, vitamin D deficiency, stress, smoking and silicone breast implants, as reviewed elsewhere[19]. The most evidence has been presented for infection, and several epidemiological studies provide evidence of an association between prior infection and subsequent development of pSS[5,116]. These studies imply that both bacterial and viral infection can increase the risk of pSS, but experimental investigations have focused mostly on viruses. Specifically, some data, such as the expression of viral antigens in the minor salivary glands of patients with pSS[117–119], implicate a role for Epstein–Barr virus (EBV) infection in driving local chronic inflammation. Intriguingly, a substantial number of pSS risk loci are potentially bound by the EBV protein EBNA2 (ref. [30]), substantiating a potential gene–environment link in the context of EBV infection. Regarding other environmental factors implicated in autoimmunity, smoking is an established risk factor for seropositive RA[120]. By contrast, smoking is not thought to increase the risk of pSS development[121–124]. Instead, in the years preceding a diagnosis, individuals who later develop pSS are more prone to stop smoking than the general population[121], and no discernible interactions have been detected between smoking and risk-related HLA alleles[121].

Female sex

The strongest known risk factor for developing pSS is female sex. The sex disparity in pSS is among the most pronounced of all autoimmune diseases, with an average 14:1 female to male ratio across geolocations and ethnicities[1,125]. The factors that underlie this difference are, however, poorly explored, and both general differences in immune regulation between women and men, as well as overlaid pSS-specific features, probably contribute[126]. The differences in immune responses between women and men in general have long been recognized[127], and they became particularly evident during the COVID-19 pandemic, with more profound antibody responses and fewer cases of severe disease occurring in women than in men[128,129]. Increasing data from large-scale analyses of gene expression in tissues[52,130,131] and cells stimulated in vitro with different classes of pathogen[132] confirm that immune responses differ substantially between the sexes. Sex hormones, sex chromosome dosage and sex-influenced regulation of disease-associated genetics have all been suggested as relevant genetic or genetically related factors for sex differences in human complex traits[133] (Fig. 5). In this section, we summarize the current understanding of these factors and their role in pSS.

Sex hormones. Differential immunomodulatory effects elicited by sex hormones have obvious potential to contribute to the sex bias in pSS[134]; however, studies on sex hormone levels in patients with pSS are remarkably limited, and the results are inconsistent[135–138]. Thus, sex hormones might contribute non-specifically to pSS as part of a general enhancement of immune responses that is more pronounced in women than in men. Indeed, oestrogen receptors are potent modulators of immune responses, including the type I interferon responses often seen in patients with pSS (reviewed elsewhere[139]).

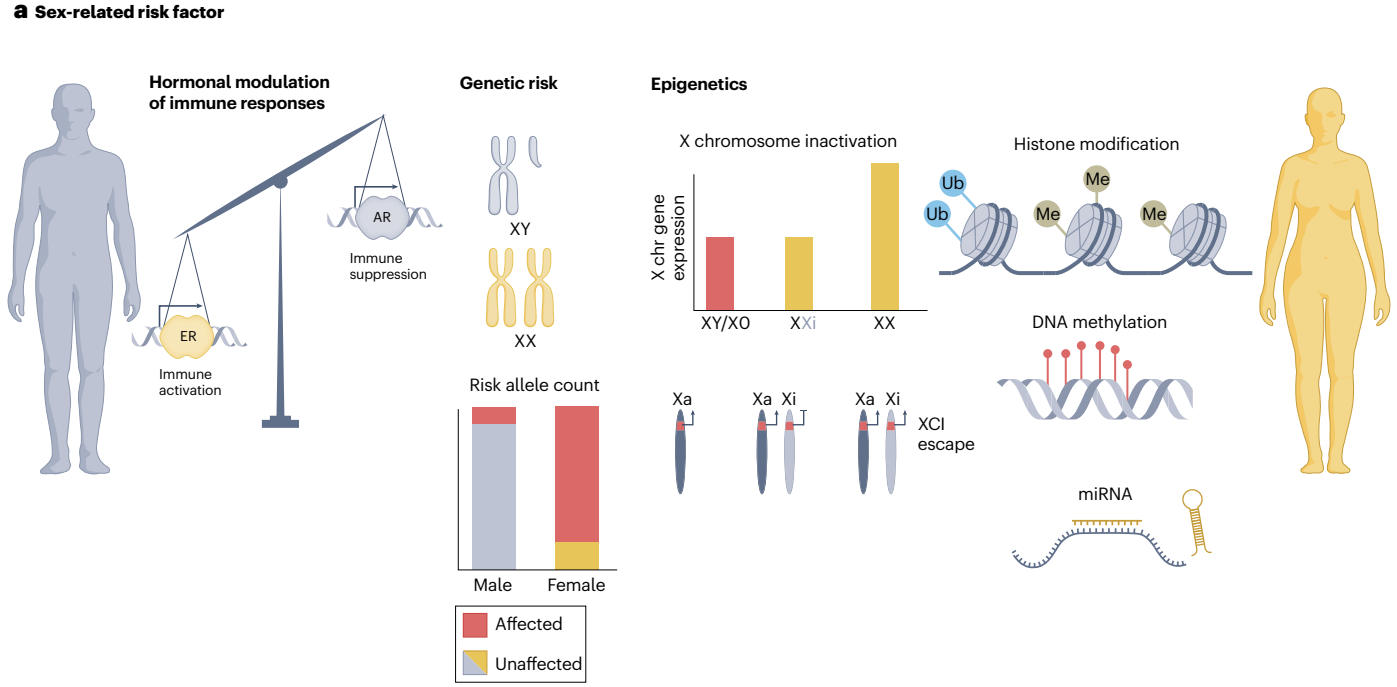
X chromosome gene dosage. Another aspect in the context of female risk of pSS is the disparity in X chromosome number between men and women, which could provide a genetic explanation for the sex bias. Indeed, many important immune genes including *TLR7*, *TLR8*, *BTK*, *FOXP3*, *IL2RG* and *CXCR3* are located on the X chromosome. Although no SNP associations with pSS have yet been identified on this chromosome[30], the importance of the X chromosome in pSS is supported by studies of aneuploidy[140]. The frequency of aneuploidy in patients with pSS is low, but several studies support an X chromosome dosage effect on risk of pSS. One study found that the frequency of men with Klinefelter syndrome (47, XXY) is higher among patients with pSS than in the general population[141]: four men with the karyotype 47, XXY were identified in a cohort of 136 men with pSS, as compared with the 1:500 reported population prevalence of this condition. In another study, women with an extra X chromosome (47, XXX) were present at a higher-than-expected rate in a cohort of patients with pSS[142]. As these women have the same levels of sex hormones as women without an extra X chromosome (46, XX), the X chromosome load rather than hormonal factors was suggested to increase the risk of pSS.

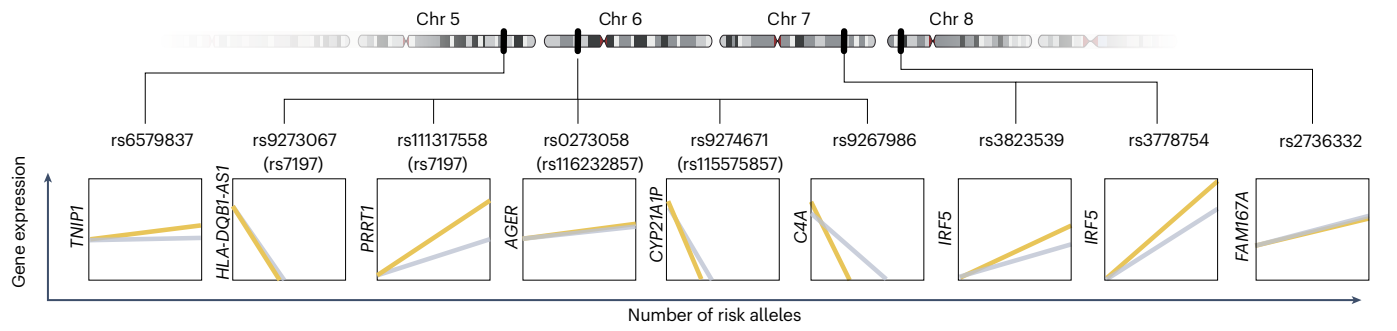
In carriers of multiple X chromosomes, the paternal or maternal X chromosome is randomly silenced in each cell during embryogenesis in an epigenetic process denoted X chromosome inactivation (XCI). Skewed XCI or escape from XCI can result in increased expression of X chromosome genes, including immune genes. Indeed, as much as 15–23% of X chromosome genes are reported to escape XCI[143]. Although data for pSS specifically is currently lacking, XCI escape of *TLR7* (ref. [144]) and *TASL*[145] is known to occur in immune cells of men with Klinefelter syndrome and in women. Both genes are implicated in SLE[146,147] and are functionally connected; indeed, TASL functions as an immune adaptor for TLR7, TLR8 and TLR9 signalling and mediates activation of IRF5 (ref. [148]). Escape from XCI is thus a potentially important genetic mechanism for sex-dependent development of autoimmunity dependent on type I interferon pathways.

Sex-influenced eQTLs. Sex differences at the DNA sequence level are restricted to the X and Y chromosomes. However, all genetic variants so far associated with pSS at genome-wide significance are located on autosomal chromosomes and thus have the same frequencies in men and women in the general population[149]. However, female carriers of these polymorphisms are more prone to develop pSS than male carriers[150], indicating that the context of 'female sex' influences the effect of these polymorphisms on promoting disease development. Disease-associated variants can have discordant effects on the expression of nearby genes in women versus men[151], known as sex-influenced eQTLs (Supplementary Box 1).

A role for sex-influenced eQTLs in complex diseases that differ by sex in terms of disease prevalence, course or severity was suggested more than a decade ago[151], but only after GWAS grew common did these large-scale studies provide the substantial data needed to support the

hypothesis[152–154]. Indeed, many genetic variants associated with pSS have genotype-dependent effects on gene expression that relate to the biological sex of the carrier. For example, *CD74* (*TNIP1* locus), *PXK*, *CTSB* (*FAM167A–BLK* locus) and *ARCN1* (*CXCR5* locus) are differentially expressed in B cells depending on the genotype and sex of the carrier[150]. Similarly, disease-associated variants in the HLA locus differentially affect the expression of *HLA-DRB5* in whole blood in a sex-dependent manner[152].





Tissue	Brain	Skin (sun exposed)	Breast	Heart	Tibial nerve	Liver	Adipose	Skin (sun exposed)	Adipose
Male	0.004	0.648	0.143	0.048	0.753	−0.397	0.133	0.277	0.119
Female	0.055	0.736	0.308	0.056	1.100	−0.924	0.206	0.390	0.109
Gen*sex	−0.520	−0.219	−0.173	−0.113	−0.378	−0.271	0.069	0.097	−0.204

Fig. 5 | Potential mechanisms connecting biological sex with risk of primary Sjögren syndrome. Sex hormones affect biological functions directly and indirectly. The figure illustrates how genetic risk factors can result in discordant effects depending on the sex of the individual. **a**, Suggested hypotheses to explain this discordance include differential hormonal modulation of immune responses, men requiring a higher number of genetic risk loci to develop disease and differences in X chromosome (X chr) dosage. Genes located on the X chromosome, including important immune genes such as *TLR7*, can escape X chromosome inactivation (XCI), resulting in higher expression of the protein in women than in men. Other epigenetic modifications can also differ between men and women, including microRNA (miRNA) expression, histone modification and DNA methylation patterns. **b**, Some single nucleotide polymorphisms (SNPs) associated with primary Sjögren syndrome (pSS) affect the expression of genes in a sex-dependent fashion (known as sex-influenced expression quantitative trait loci (eQTL)). Variants associated with pSS with discordant effects on gene expression between men and women that reach a particular significance threshold ($P < 0.05$) for sex–genotype interactions are included (data taken from the Genotype-Tissue Expression (GTEx) database). All variants in high linkage disequilibrium with the Sjögren syndrome-associated variants were considered. Variants reported as associated with pSS (Table 1) are included in parenthesis if a sex-eQTL effect was identified for a linked variant. The table summarizes the tissue the effect was identified in, the effect size (expressed as a regression coefficient) in men and in women, and the genotype-by-sex (gen*sex) interaction effect size. AR, androgen receptor; ER, oestrogen receptor; Me, methyl group; Ub, ubiquitin.

Large-scale efforts such as the Genotype-Tissue Expression (GTEx) consortium (see Related links) have made possible the examination of sex-influenced eQTLs in many different tissues[155]. Of the 27 independent pSS-associated genetic signals, six had notable sex-specific effects on the expression of several genes, including *TNIP1*, *IRF5* and *C4A* in five tissues (Fig. 5). Sex-specific differences have been further studied during immune activation, in which cells from men and women were exposed to lipopolysaccharide to identify sex-specific responses to microbial stimuli[156]. Interestingly, seven genes in pSS-associated loci showed significant sex by treatment interactions, including four HLA genes, *IRF5, OAS1* and *IKZF1* (ref. [156]). Overall, eight of the 27 loci independently associated with pSS contain sex-influenced eQTLs, clearly demonstrating that the biological sex of an individual can influence the effect of a risk allele on gene expression and subsequent outcomes. Notably, in 2020, researchers confirmed the interaction between sex and pSS-associated genetic variants of the C4 locus[157], firmly supporting the relevance of sex-influenced eQTLs not only for gene expression levels, but also for disease development.

Sex influence on epigenetic regulation. An emerging area of investigation is the involvement of epigenetic mechanisms in sex-influenced eQTLs. The X chromosome is rich in miRNA genes, whereas the Y chromosome contains relatively few miRNAs[158], suggesting that miRNAs or other epigenetic factors have a role in mediating sex differences in pSS. Sex is known to influence autosomal DNA methylation[159], and evidence suggests that oestrogen can regulate both methylation and miRNA expression (reviewed in[160]). Sex-influenced QTLs that regulate the expression of miRNA (known as miRNA eQTLs) have been identified and implicated in autoimmune diseases[161]. Various miRNAs, including miR-146s, are already implicated in the phenotypes commonly seen in pSS such as parotid swelling and dry eyes[85], and whether such epigenetic mechanisms differ by sex is worth exploring.

Genetically inferred therapeutic targets

Genetic, epigenetic and mechanistic studies have greatly expanded our understanding of the immunopathogenic processes that underlie pSS. Nevertheless, no immunomodulatory treatments that can affect the activity and/or progression of the disease are yet available[12]. Ongoing and completed randomized controlled trials (RCTs) generally use targeted approaches aimed at depleting specific cell populations, inhibiting co-stimulation, blocking cytokine–receptor interactions or targeting kinases important for intracellular signalling. Therapies evaluated in major RCTs for pSS (trials with >100 patients) include infliximab (a TNF inhibitor)[162], rituximab (an anti-CD20, B cell-depleting antibody)[163,164], abatacept (a fusion protein that blocks CD28–CD80/CD86 co-stimulation)[165], tocilizumab (an IL-6 inhibitor)[166] and ianalumab (a BAFF inhibitor and B cell-depleting antibody)[167] (Fig. 6). Of these trials, only ianalumab met the primary end point of the study[167]. Numerous smaller RCTs and open label studies have also been carried out, with varying degrees of success (summarized elsewhere[12]). The failure of clinical trials in pSS could be due to the selection of therapeutic target, factors such as disease heterogeneity, choice of clinical end point, difficulties in distinguishing between organ damage and disease activity and/or power limitations. Novel responder indices and end point measures have been developed for pSS, which could benefit future studies[168,169].

What can we learn from genetic and epigenetic studies regarding treatment approaches? As summarized in the section on 'Implicated pathogenic processes', results from these studies implicate four major pathogenic processes in pSS: TLR and interferon signalling; lymphocyte regulation; antigen presentation; and target tissue maintenance (Figs. 4 and 6). In this section, we discuss current and emerging therapeutic strategies that target these processes. Although the first two processes contain main targets of current treatment approaches, the latter two remain underexplored.

TLR signalling and interferon pathways

Genetic associations as well as the frequent detection of hypomethylation at interferon-regulated genes underscore the importance of TLR and interferon signalling in pSS. Activity of the type I interferon system is high in the blood and target tissue of most patients with pSS[13]. As such, several approaches have been developed to target these pathways. For example, the JAK inhibitor tofacitinib inhibits both type I and type II interferon, and a randomized trial in pSS is currently recruiting[170]. Notably, in ATG5-deficient 3D-acini (a relevant model given the previously identified genetic associations at *ATG5* (ref. [30])), tofacitinib could suppress IL-6 production caused by deficient autophagy[171]. Another JAK inhibitor, baricitinib, indicated possible efficacy in a small pilot study involving 11 patients with pSS[172].

Regarding the genetic association at *TYK2*, selective inhibition of TYK2 in pSS is a potential therapeutic avenue[173], and this strategy is currently being tested in SLE using deucravacitinib[174]. Blockade of IL-12 and IL-23, which results in inhibition of the type II interferon pathway, can be achieved using the monoclonal antibody ustekinumab and is currently being evaluated in a pilot trial in pSS[175]. Targeting of the BDCA2 antigen on plasmacytoid dendritic cells (a cell source of type I interferon) using monoclonal antibodies has been evaluated in a phase I trial in patients with cutaneous lupus erythematosus, with preliminary results suggesting some efficacy[176], highlighting another possible approach for the treatment of pSS.

Finally, the monoclonal antibody anifrolumab, which targets the type I interferon receptor IFNAR1, restored gene expression-based type I interferon scores to normal levels after 12 weeks of treatment in patients with SLE[177], and was approved in 2021 for the treatment of moderate to severe SLE[178]. A phase IIa proof-of-concept trial of anifrolumab for evaluation as a potential treatment of pSS is in recruitment phase[179]. From an epigenetic perspective, one question of interest is whether treatment with anifrolumab influences hypomethylation at interferon-regulated genes. Altogether, targeting TLR and type I interferon signalling in pSS constitutes an attractive approach and can be achieved in many ways.

Lymphocyte regulation

Most proteins, as well as the miRNA miR-146a, that are encoded by pSS genetic risk loci are involved in lymphocyte regulation (Fig. 4). Additionally, variants at genes involved in TLR and interferon signalling might contribute to augmented activation of B cells and T cells, and polymorphisms in *FAM167A–BLK*, *PRDM1* and *IKZF1* might have direct effects on B cell lineages, supporting the potential of B cell-targeted therapies.

Many small studies as well as two large RCTs have evaluated the monoclonal anti-CD20 B cell-depleting antibody rituximab in patients with pSS[12]. Although saliva flow rates improved, the large RCTs did not meet their primary end points[163,164]. Nevertheless, in clinical practice rituximab is considered effective for treating certain manifestations including cryoglobulinaemia-associated vasculitis[11]. Second-generation anti-CD20 drugs such as obinutuzumab, which mediate more efficient B cell depletion than rituximab, have been developed but have not yet been tested in pSS.

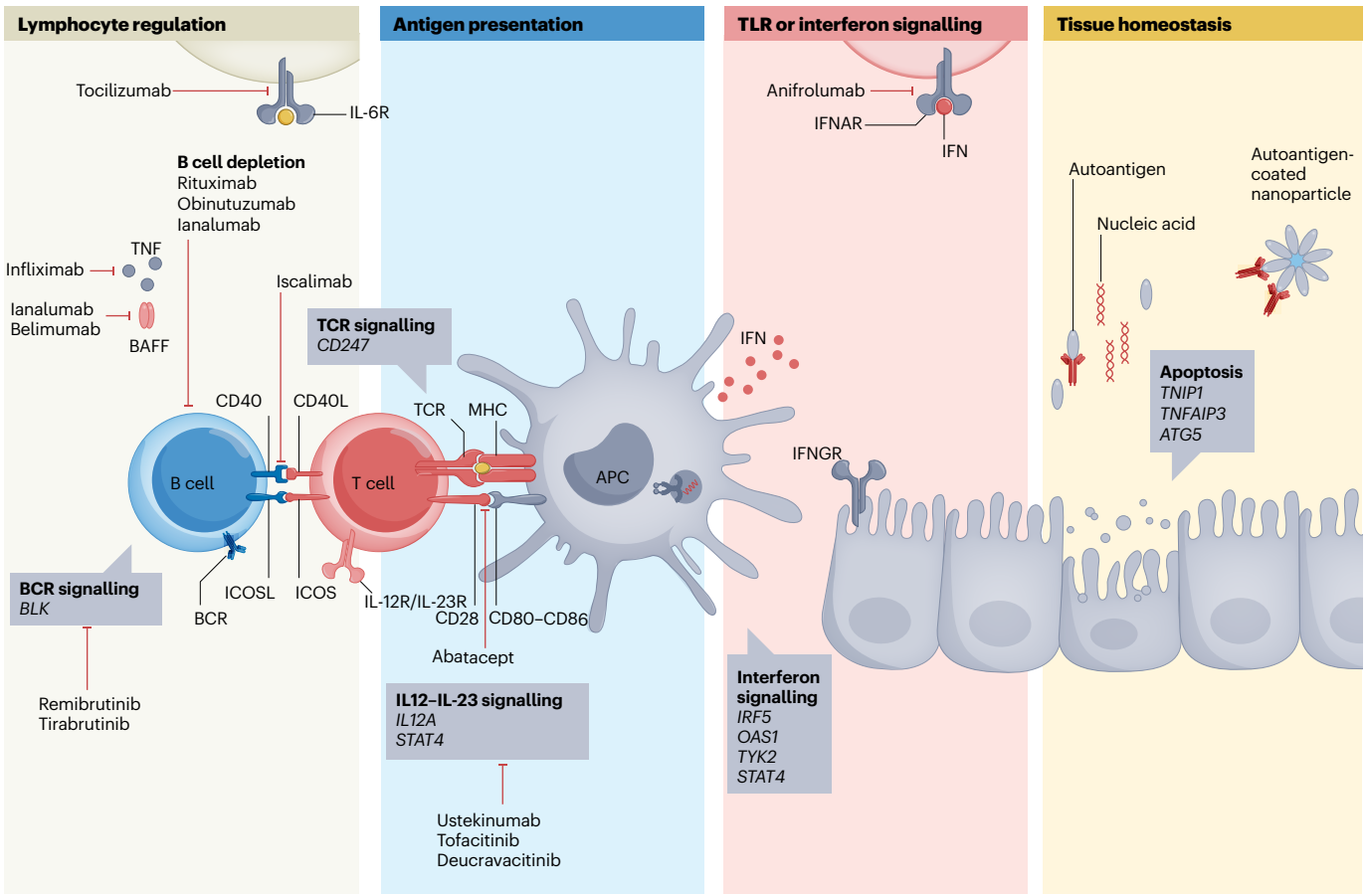


Fig. 6 | Treatment targets implicated by genetic studies in primary Sjögren syndrome. The processes implicated by genetic studies in the pathogenesis of primary Sjögren syndrome (pSS) include lymphocyte regulation, antigen presentation, Toll-like receptor (TLR) or interferon (IFN) signalling and tissue homeostasis (including apoptosis and autophagy). Selected pSS risk genes involved in these processes are indicated in boxes. These processes (particularly lymphocyte regulation and TLR or interferon signalling pathways) include targets of current and emerging therapies. APC, antigen-presenting cell; BAFF, B cell-activating factor; BCR, B cell receptor; TCR, T cell receptor.

An alternative approach to B cell targeting is to block B cell activation. BAFF is an important cytokine in pSS pathogenesis owing to its many B cell-promoting properties, and the anti-BAFF monoclonal antibody belimumab is an approved treatment for SLE[180]. In one open label study of belimumab in 30 patients with pSS, the primary end point was reached in 60% of patients[181]. In a randomized phase II study evaluating co-administration of belimumab with rituximab, depletion of $CD20^+$ B cells in minor salivary gland biopsies and $CD19^+$ B cells in the periphery was greater compared with monotherapy with rituximab or belimumab alone, and reduction in ESSDAI scores was numerically greater in the combination group, highlighting the potential benefit of combined therapy[182]. Another approach has been to block transmembrane activator and cyclophilin ligand interactor (TACI), which is a receptor for both BAFF and a proliferation-inducing ligand (APRIL), and a phase II trial of telitacicept (a TACI–Fc fusion protein) has been completed, but the results have not yet been published[183,184]. In 2022, a phase IIb dose-finding trial of ianalumab (an anti-BAFF receptor monoclonal antibody) was the first large RCT in pSS to reach its primary end point (reduction in ESSDAI at 24 weeks)[167]. Future approaches could involve specific targeting of pathogenic B cells (as discussed in the next section), but means to accomplish such target specificity is still needed. In terms of other potential B cell targets, *FAM167A* is expressed in peripheral B cells and the encoded protein is present in plasma cells in the minor salivary glands of patients with pSS[92], yet the function of this intracellular protein remains unknown, and should therefore be further studied and assessed as a potential therapeutic target.

Several genetic signals such as those from *CXCR5*, *CD247* and the HLA locus point to the importance of B cell–T cell interactions, which can be targeted in several ways. In pSS, two phase III RCTs assessed blockade of the CD28–CD80/86 axis using the CTLA4–immunoglobulin fusion protein abatacept, but both studies failed to reach the clinical end points[165,185]. Another approach has been to block CD40–CD40L interactions using iscalimab (an anti-CD40 antibody), an approach that showed preliminary success in terms of efficacy in a proof-of-concept study[186], and further trials targeting this interaction are underway[187]. A third approach has been to block the interaction of inducible T cell co-stimulator (ICOS) with its ligand, ICOSL, using a monoclonal antibody (MEDI5872); however, this approach did not result in improvement in disease activity in a phase IIb study in pSS[188]. Interestingly, the promoter region of *CXCR5* is hypomethylated in B cells of patients with pSS[189],

and a pSS-associated variant near *CXCR5* has an eQTL effect in B cells and seems to influence the cell surface expression of CXCR5; therefore, targeting the CXCR5–CXCL13 chemokine axis is another potential therapeutic strategy that remains to be explored[94].

pSS associations at *TYK2* and *BLK* suggest that intracellular kinases are important in pSS-related disease pathways, which could be targeted with small-molecule inhibitors. For example, Bruton's tyrosine kinase (BTK) has an important role in signalling downstream of the B cell receptor[190]. Mutations in *BTK* cause the immunodeficiency disease X-linked agammaglobulinaemia[191], and overexpression of BTK in mice causes an autoimmune phenotype[192]. A phase II trial of the BTK inhibitor remibrutinib in pSS showed that this drug has a favourable safety profile and potential efficacy (as assessed by reduction in ESSDAI score and improvement in salivary flow rates at 24 weeks)[193]. By contrast, a phase II trial that included assessment of tirabrutinib, another BTK inhibitor, found no indication of efficacy in pSS[194]. Other approaches for blocking pathways crucial for lymphocyte activation include inhibition of one of the signalling molecules spleen tyrosine kinase (SYK) or phosphatidylinositol 3-kinase (PI3K); however, inhibitors of these kinases have thus far shown no obvious efficacy in small trials[187,194].

Antigen presentation

Although the HLA locus has long been characterized as the major genetic risk locus in pSS, antigen presentation remains a challenge to target therapeutically. Future approaches to treat autoimmunity include antigen-specific immunotherapy, which aims to specifically target the pathogenic immune cells. This concept involves specifically targeting autoreactive B cells and T cells through the administration of tolerogenic peptides, the use of tolerizing antigen-specific vaccines, administration of tolerogenic dendritic cells, clearance of pathogenic autoantibodies and/or the use of chimeric antigen receptor (CAR)-transduced T cell therapy[195]. For example, in various mouse models of autoimmunity, administration of nanoparticles coated with autoimmune-associated antigens bound to MHC class II peptides could shift disease-primed cells into regulatory cells[196]. Antigen-specific immunotherapy relies on adequate selection of autoantigens, and whether the known autoepitopes in pSS, such as those of the Ro52 and Ro60 proteins[197], would enable disease modification remains to be explored.

Target tissue maintenance and multiple target strategies

Dysregulated apoptosis of salivary gland epithelial cells occurs in pSS[198]. Whether this process is an important initial event that leads to development of the autoimmunity and disease is unclear, but exploring this process further might uncover treatment options for the very early phase of disease, with the prospect of preventing tissue destruction.

Given the polygenic nature of disease risk in pSS, targeting a single cell type or signalling pathway might be insufficient, and targeting multiple processes could be necessary. Hence, various trials have tested drugs that modulate several disease pathways. For instance, the tetravalent bispecific antibody tibulizumab targets both IL-17A and BAFF[199]. Although targeting multiple pathways might prove to be more efficient than targeting a single pathway, a higher risk of adverse events could be expected.

Targeting DNA methylation

Modification of DNA methylation is a potential therapeutic intervention for various diseases, as exemplified by successful employment of such drugs in the field of immuno-oncology[200]. Available drugs that modify DNA methylation are employed for the treatment of various cancers[200]. However, these drugs, including azacytidine and decitabine, are DNA methyltransferase inhibitors, and they function in a nonspecific manner to reduce genomic DNA methylation, which could be counterproductive for the treatment of pSS, given that pSS-associated genes tend to be hypomethylated. Indeed, the drugs hydralazine and procainamide, which inhibit DNA methylation[201], have long been known to confer a high risk of triggering drug-induced SLE[202]. To date, epigenetic modifiers have not been tested in pSS but constitute an interesting future treatment approach.

Conclusions

Emerging genetic and epigenetic data in pSS highlight the polygenic nature of the disease, and the influence of environmental triggers as well as female sex on pSS development. The identified genetic and epigenetic signals hold promise for addressing the many unmet clinical needs in pSS, including possibilities for earlier diagnosis, novel tools for patient subphenotyping, prognostic markers for comorbidities such as cardiovascular disease and lymphoma, and, ultimately, efficacious treatment to ameliorate disease activity, stop disease progression and rescue organ function. As outlined in this Review, the genetic and epigenetic findings point towards four interconnected immune processes of central importance to disease development and pathology. Within these processes, some therapeutic prospects have already been identified and attempted, but many potential targets remain to be explored. Interestingly, calculating genetic or epigenetic risk scores already holds potential for better stratification of disease subtypes and could be considered in future clinical drug trials[30].

Notably, only a few epigenetic signals overlap with identified genetic risk loci in pSS. This lack of overlap suggests that many genes that increase the risk of pSS function upstream of cellular events and lead to epigenetic changes and differences in gene expression but are not epigenetically modified themselves and could thus constitute potential molecular targets. Strong evidence highlights the involvement of TLR and interferon signalling, including disease associations with genetic variants of genes in these pathways, as well as the extensive hypomethylation of interferon-regulated genes. Both genetic and epigenetic findings also support the strong association of disease with the HLA locus, which has been recognized for decades. Although many drugs currently in the pipeline are aimed at TLR and interferon pathways, treatments specifically targeting antigen presentation or aimed at tolerance induction have not been successfully developed for pSS and constitute future potential areas for development.

Epigenetic alterations differ between tissues and cell types, but a pattern in pSS is emerging, involving extensive alterations of DNA methylation in both B cells and target tissue. A future challenge will be to identify drugs that can specifically reverse these epigenetic changes, unlike the currently available drugs, which function in a largely nonspecific manner. Other epigenetic treatment prospects in immune cells and target tissue include modulation of non-coding RNAs and alteration of histone acetylation patterns as well as nucleosome positioning. Also, the emerging field of epitranscriptomics, which refers to post-transcriptional modifications of RNA[203], deserves attention but has not yet been studied in pSS.

Beyond indicating which processes could be of relevance to target, knowledge of the underlying genetics and epigenetics can facilitate earlier diagnosis through risk scores and enable subphenotyping of patients. Future studies performed in larger cohorts that include sequencing of RNA and DNA as well as use of other novel technologies and application of sophisticated analytical approaches

to combine data obtained by these high-throughput technologies is expected to greatly enhance our understanding of pSS and open novel possibilities to address the unmet needs of the disease in the upcoming years.

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