HHS Public Access

Author manuscript

Semin Liver Dis. Author manuscript; available in PMC 2015 December 18.

Published in final edited form as:

Semin Liver Dis. 2015 November ; 35(4): 392–401. doi:10.1055/s-0035-1567831.

GWAS in Primary Biliary Cirrhosis

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Abstract

Genome wide association studies (GWAS) have been a significant technological advance in our ability to evaluate the genetic architecture of complex diseases such as Primary Biliary Cirrhosis (PBC). To date, six large-scale studies have been performed which identified 27 non-HLA risk loci associated with PBC. The identified risk variants emphasize important disease concepts; namely, that disturbances in immunoregulatory pathways are important in the pathogenesis of PBC and that such perturbations are shared among a diverse number of autoimmune diseases – suggesting the risk architecture may confer a generalized propensity to autoimmunity not necessarily specific to PBC. Furthermore, the impact of non-HLA risk variants, particularly in genes involved with IL-12 signaling, and ethnic variation in conferring susceptibility to PBC have been highlighted. While GWAS have been a critical stepping-stone in understanding common genetic variation contributing to PBC, limitations pertaining to power, sample availability, and strong linkage disequilibrium across genes have left us with an incomplete understanding of the genetic underpinnings of disease pathogenesis. Future efforts to gain insight into this missing heritability, the genetic variation that contributes to important disease outcomes and the functional consequences of associated variants will be critical if practical clinical translation is to be realized.

Keywords

GWAS; PBC; autoimmunity; genetics

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INTRODUCTION

Primary biliary cirrhosis (PBC) is a female predominant autoimmune liver disease affecting 1 in 1000 women over the age of 40[1]. It is characterized by chronic cholestasis, specific anti-mitochondrial antibodies (AMAs), destruction of the intralobular bile ducts, and can progress to liver failure[2]. Ursodeoxycholic acid (UDCA) is the only approved therapy for PBC and is beneficial to many patients[3]; however, approximately one-third of those treated do not respond well to UDCA and tend towards progressive liver disease requiring transplantation[4].

As with most autoimmune diseases, PBC is genetically complex. That is, individual alleles are not likely deterministic per se, but rather act by modifying risk through subtle effects on disease-specific biological processes in context of the internal milieu and environmental exposures. Frequent co-expression of PBC with other autoimmune disorders suggests the susceptibility backgrounds influencing disease expression are shared to some extent. However, the mechanisms underlying these observations remain obscure. Multiple lines of evidence emphasize the importance of genetic predisposition in the development of PBC, including increased PBC prevalence in first-degree relatives (FDRs) of affected patients[5] and high concordance in monozygotic twins[6]. Furthermore, a large study from the UK reported a sibling relative sibling relative risk (λ_s) of 10.5[7] and our group found a high prevalence of AMA positivity in FDRs of affected probands[8]. Despite this prior knowledge, significant advancements in PBC genetics have been slow to come, hampered by the rarity and late onset of disease. Until recently, genetic research in PBC was limited to surveys of candidate genes selected by biologic plausibility or known association with other autoimmune diseases. These studies, while an important step, were universally plagued by poor gene coverage and insufficient power to detect modest effects.

Genome wide association studies (GWAS) have significantly advanced our ability to evaluate the genetic architecture of complex diseases, with particular applicability to genetic variants that are common in the population (i.e. those with minor allele frequency (MAF) of > 5%). Current iterations of GWAS platforms effectively interrogate millions of single nucleotide polymorphisms (SNPs) across the entire genome, and are extendable through imputation to existing sources of genetic diversity data such as the 1,000 genomes project[9]. While the GWAS approach has matured, important limitations pertaining to power, sample availability, linkage disequilibrium and population differences remain; leaving us with an incomplete accounting of genetic contributors to disease. Moreover, the majority of detected GWAS associations have modest effect sizes (odds ratios in the range of 1.1–1.7) and the biological effects behind most of the associated variants remain undefined[10]. Thus, it is important to recognize that while GWAS have been critically informative, functional studies will be needed to identify precise causal variants and define their biologic effects.

PRE-GWAS: FOCUS ON IMMUNOLOGY AND CANDIDATE GENES

Prior and emerging knowledge of pathogenic disease mechanisms in PBC is a necessary basis for informed interpretation of GWAS findings. In PBC, past efforts have widely focused on features of immunology, and a broad range of immune cell types spanning both

the innate and adaptive arms have been implicated (recently reviewed)[2]. The immunodominant PBC autoantigen is the E2 subunit of the pyruvate dehydrogenase complex (PDC-E2), a mitochondrial enzyme that is the target of disease-specific AMAs[11]. T-cells ($CD4^+$ and $CD8^+$) auto-reactive to PDC-E2 are enriched in the liver of PBC patients[12,13], and produce high levels of the cytokine interferon-γ, suggesting T-helper 1 (T_H1) polarization and a role for cellular immunity in mediating liver damage in PBC[14]. Despite the ubiquitous nature of PDC-E2, only the small intralobular bile ducts are targeted in patients with PBC[15,16]. This specificity derives from the unique nature of apoptotic protein degradation in biliary epithelial cells, which leaves an immunogenic form of PDC-E2 intact within the apoptotic bleb, a process that is not restricted to PBC[17,18]. Current consensus is that environmental factors such as certain infections or chemical exposures, in concert with an autoimmune-permissive genetic background, are the main contributors to loss of tolerance and conversion to frank autoimmunity in PBC[19].

Prior to GWAS, genetic studies in PBC primarily focused on candidate genes selected based on the existing immunological knowledge. The most successful of these efforts was the study of human leukocyte antigen (HLA) genes located in the gene-dense and highly polymorphic major histocompatibility complex (MHC) at chromosome 6p21. HLA genes encode molecules responsible for antigen presentation, and thus, are integral in distinguishing self from non-self and enforcing immune tolerance[20]. The most commonly detected alleles from candidate gene studies were within the HLA DRB1*08 family, specifically DRB1*0801 in European and North American Caucasian populations[21–23] and the DRB1*0803 in the Japanese[24], suggesting ethnic variation in disease susceptibility. As well, DRB1*11 and HLA DRB*13 were found to be protective in studies from Italy and the UK[22,25].

A number of non-HLA candidate gene studies in PBC interrogated genes known or suspected to be involved with autoimmunity including *TNF, CTLA4, PTPN22, PDCD1, IL1, IL2, IL10*, toll like receptors and the vitamin D receptor[26–34]. Many of these studies were limited by inadequate power and poor gene coverage (often just a single SNP) and there was little correlation between studies. Importantly, none of the genes investigated in the candidate-gene era have demonstrated robust findings in GWAS of PBC.

FINDINGS FROM GWAS

To date, four GWAS and two Immunochip studies using well-characterized patient cohorts from North America, Europe or Japan have been performed for PBC. The strongest statistical associations have consistently been at the HLA locus, confirming its importance in the pathogenesis of disease. Dozens of new PBC-associated HLA variants have been identified by GWAS, particularly at the DRB1, DQA1 and DQB1 loci, but specific causal alleles have been challenging to define[35]. Analyses incorporating GWAS data have suggested that different HLA types may contribute to immunologic phenotypes, with SNPs at the *HLA-DPB1* locus being strongly associated with disease in PBC patients who test positive for anti-sp100 antibodies but not in anti-sp100 negative individuals[36]. Similarly, a Japanese study reported that HLA-DRB1*0405 predisposed to anti-gp20 positivity and *0803 was associated with anti-centromere antibodies[37]. Notwithstanding these

observations, a notable lesson from GWAS is that in PBC the HLA risk alleles are relatively uncommon among patients (often less than 15%) and the effect sizes, while statistically robust, are not striking relative to other autoimmune disease[38]. This suggests that though HLA is clearly an important contributor to PBC risk, the non-HLA loci are likely to play an equally critical role.

At present, 27 non-HLA genetic loci have demonstrated genome-wide significant associations with PBC (Table 1). The first GWAS, from Canada, identified SNPs at three loci, namely HLA, *IL12A* which encodes IL-12 p35, and *IL12RB2* which encodes IL-12 receptor β2[39]. Further fine-mapping efforts implicated a five allele haplotype at the 3′ flank of the *IL12A* gene as significantly associated with PBC, though the precise causal alleles remain unknown. Importantly, this study began to shed light on the potential importance of the IL-12 signaling axis in the pathophysiology of PBC. The second effort that used both Italian and Canadian subjects, confirmed associations from the initial GWAS, and identified three additional disease-associated loci mapping to regions containing *IRF5-TNPO3, IKZF3*, and *SPIB*, each of which plays a role in immunoregulation[40]. The largest PBC GWAS to date, which included more than 1800 cases and 5000 controls from the UK, identified 12 additional non-HLA loci reaching genome-wide significance and confirmed that all previously identified loci showed at least suggestive levels of association with PBC[41]. When data were combined with the Italian cohort in a meta-analysis, a further three novel loci were identified at a genome wide level of significance[40]. The most recent GWAS, which was performed in a Japanese population, identified two novel risk loci implicating the genes *TNFSF15* and *POU2AF1*. Of interest, only five previously identified non-HLA loci (*IL7R, IKZF3, CD80, STAT4* and *NFKB1*) from the North American and European GWAS were found to be associated with PBC at genome-wide or suggestive levels of significance[42]. Notably, despite the *IL12A* and *IL12RB2* loci being among the strongest non-HLA associations in the Caucasian studies, they were not significantly associated with PBC in Japanese patients. This finding serves to highlight the importance of ethnic differences in the way common genetic variation impacts susceptibility to complex disease.

Two additional studies were performed using the Immunochip platform, which was designed as a tool to facilitate fine mapping of 186 known autoimmune loci[43]. The larger of the two studies, from the UKPBC consortium, added three new loci, implicating the genes *SH2B3, MAPT*, and *TYK2*, to the list of GWAS-level PBC associated variants[44]. In our study, which utilized American, Canadian and Italian cohorts, a novel association implicating the *TNFSF11* gene was identified and many previously known associations were again confirmed[45]. Taken together, this collective body of evidence has implicated multiple genes in the pathogenesis of PBC, many of which have also demonstrated association with other autoimmune diseases[35]. Key among these are genes influencing IL-12 signaling.

IL-12 GENETICS IN PBC

The list of genes identified through GWAS has emphasized the importance of immunoregulation in the pathogenesis of PBC (Table 2); and several potentially important pathways including antigen presentation, T and myeloid cell differentiation, and B cell function have been implicated as contributing to disease[46]. T lymphocyte differentiation and

T_H1 responses in particular, have been associated with several autoimmune diseases and may be involved in the development of auto-reactive T_H1 cells associated with PBC[47]. The IL-12 cytokine family, which includes IL-12, IL-23, IL-27 and IL-35, is a diverse group of heterodimeric molecules sharing protein chains and conferring both positive and negative immunoregulation[48] (Figure 1). IL-12 is a major cytokine involved in the development of T_H1 responses[49], and as mentioned, variants at the *IL12A* and *IL12RB2* loci have been among the strongest and most reproducible associations with PBC in GWAS efforts[48]. Functional IL-12 is comprised of two subunits, IL-12 p35 (encoded by the *IL12A* gene) and IL-12 p40 (encoded by the *IL12B* gene) which interact with the cell–surface IL-12 receptor (composed of the IL-12 receptor β1 and β2 chains) on $CD4^+$ T cells to induce Jak-STAT signaling leading to activation of a T_H1 response[50]. Notably, genetic loci containing components of Jak-STAT signaling downstream of IL-12 (*TYK2* and *STAT4*) have also demonstrated significant associations with PBC. Engagement of intact IL-12 with its receptor modulates the immune response by evoking interferon-γ (IFN-γ) production, which enforces expression of IL-12 receptor β2 and inhibits induction of proinflammatory T-helper 17 (T_H17) cells by IL-23, which also uses the IL-12 p40 subunit and IL-12 receptor β1 chain[19]. Of interest, the components of IL-12 that demonstrate association with PBC, IL-12 p35 (*IL12A*) and IL-12 receptor β2 (*IL12RB2*), are also components of IL-35, an IL-12 family member with negative-regulatory activity which blocks T_H1 and T_H17 development and supports proliferation of naturally-occurring and inducible subsets of regulatory T cells[51]. Overall, the complexity of the IL-12 family, combined with lack of knowledge regarding the functional consequences of the observed genetic associations, obscures the precise mechanisms of IL-12 mediated pathogenesis in PBC.

Several other loci identified through GWAS including those containing *IRF5*, *SOCS1*, *NFKB1*, and *TNFRSF1A* suggest that pathways upstream of IL-12 production may be relevant to PBC[52]. For instance, interferon regulatory factor 5, the protein product of the *IRF5* gene, interacts with NF-κB to cause expression of a number of T_H1 cytokines, including IL-12[53]. In addition, *IRF8* encodes a transcription factor that binds to the IL-12 promotors to modulate IL-12 and IFN-γ production[52]. In the Japanese GWAS, *TNFSF15* was implicated, which interacts with death receptor 3 to promote T_H1 and T_H17 expansion and synergizes with IL-12 and IL-18 to promote IFN-γ production[42]. Thus, though the specific IL-12 loci were not significantly associated with PBC in this cohort, identification of *TNFSF15* and *STAT4* as PBC susceptibility genes may indicate that IL-12 signaling is also involved in the pathogenesis of PBC in the Japanese population.

SHARED LOCI IN AUTOIMMUNE DISEASE

Nearly one-third of patients with PBC are also affected by another autoimmune disease[54]. In keeping with this observation, the vast majority of SNPs implicated in PBC have also been found to be associated with other autoimmune diseases (Table 2). For example, SNPs within the *IL12A* gene have been associated with celiac disease[55], and variants at the *STAT4* locus (encoding a transcription factor critical to IL-12 signaling) have been associated with an increased risk of rheumatoid arthritis (RA), systemic lupus erythematosus (SLE)[56], and Sjogren's syndrome[57], among others. NF-κB is a transcription factor that is activated in several autoimmune disorders including RA, multiple sclerosis (MS) and asthma, and

regulates expression of many genes involved in the immune response[58]. Several loci containing genes involved in NF-κB activation have been associated with PBC including 4q24 which contains the *NFKB1* gene itself, as well as 22q13 (*TAB1*), 12p13 (*TNFSF1A*), 3q13 (*CD80*) and 11q13 (*RPS6KA4*)[41]. The role this pathway plays in disease-specific manifestations is unclear, but its potential importance in PBC is suggested by evidence that NF-κB action modulates the balance of survival and apoptosis in activated stellate cells[59] and NF-κB p50 knockout mice show aggressive hepatic inflammation and fibrosis[60]. Furthermore, in addition to their association with PBC, SNPs within a gene rich region on chromosome 17, particularly in the *IKZF3* gene, have also been associated with T1DM[61], Crohn's disease (CD)[62], and ulcerative colitis (UC)[63,64]. *IKZF3* encodes IKAROS family zinc finger 3, a transcription factor that prevents apoptosis of IL-2 deprived B cells, regulates B cell activation, and has been associated with a lupus like syndrome in *IKZF3* deficient mice[35]. Ultimately, the shared association of several SNPs among diverse autoimmune diseases suggests their pleiotropic effects and emphasizes that there are few disease-specific genetic associations in PBC, at least among common SNPs amenable to detection by GWAS. Whether organ-specificity in autoimmunity is the result of untested rare genetic variants, history of environmental exposures, epiphenomenon or some combination of factors remains to be determined and is the current challenge.

IMPACT OF GWAS ON PBC RESEARCH

Advancing our understanding of the genetics of PBC beyond what has been learned from GWAS, will involve complimentary approaches to investigation using animal models and next generation sequencing. Over the last several years, multiple spontaneous and inducible murine models of PBC have been developed that demonstrate characteristic serological, biochemical, and histological features of PBC and have provided valuable insight into the immunobiology of disease[65–68]. Knockout models of IL-12 subunits and associated downstream signals are particularly interesting in light of the GWAS-based evidence for the important role of this pathway in PBC. The dnTGFBRII mouse model results in transforming growth factor beta deficiency, which causes pleiotropic immunologic abnormalities including cholangitis, colitis, and early death[69,70]. Using this model, Yoshida *et al*. demonstrated that knockout of the IL-12 p40 subunit was associated with reduced levels of inflammatory cytokines, immune cell infiltration and bile duct damage[71], whereas p35 knockout mice had liver inflammation and bile duct damage that was similar in severity to the control dnTGFBRII mice, though with delayed onset[72]. IL-12 $p35^{-/-}$ mice underwent a distinct cytokine profile shift from T_H1 to T_H17 and also demonstrated significant periportal fibrosis, suggesting the contribution of the T_H17 family to progressive fibrosis in this model. The same group developed an induced model of PBC, using C57BL/6 mice, which developed high titer AMAs, portal inflammation, and autoimmune cholangitis when immunized with 2-octynoic acid (2-OA) coupled to bovine serum albumin[73,74]. Interestingly, in gene-deleted knockouts of this model, significantly less portal inflammation was observed in IL-12 $p40^{-/-}$ mice compared to IL-12 $p35^{-/-}$ or IL-12 $p19^{-/-}$[65], suggesting the potential role of an environmental trigger in development of disease amidst a permissive genetic background.

Despite advances in our understanding of the genetic contribution to disease in PBC, it is estimated that only about 15% of PBC heritability has been explained, partly because GWAS approaches are underpowered to detect rare genetic variation that could contribute to disease[44]. Though common variants likely play a significant role in PBC pathogenesis, it is plausible that highly-penetrant rare genetic variants with strong biological effect, non-SNP structural changes such as copy number variants or epigenetic modifications, and gene-gene or gene-environment interactions could account for the as yet undetermined "missing heritability" not explained by GWAS. Identifying rare genetic variants will require the use of next generation approaches including whole exome and whole genome sequencing; and for the time being, while costs and data handling capabilities pose significant limitations, targeted approaches using study designs with individuals at phenotypic extremes or family based studies with multiple affected relatives are perhaps a more practical and cost effective next step[75]. While initial application of these methods is likely to still leave a significant portion of heritability unexplained due to the small numbers of individuals used in such studies and the high likelihood for allelic heterogeneity within deleterious loci[76], important lessons and concepts are still likely to emerge akin to those learned through initial GWAS efforts.

CLINICAL IMPACT OF GWAS ON PBC

A significant gap exists between the genetic information collected to date and its practical translation into the clinic – though efforts are undergoing to bridge this space. Recently, Tang *et al*. utilized 26 known PBC risk loci identified in GWAS to calculate a weighted genetic risk score (wGRS) in order to evaluate the ability of GWAS SNPs to predict disease in two independent cohorts[77]. The wGRS showed good ability to identify individuals at risk for developing PBC, with an area under the curve of 0.72 (95% CI 0.706–0.735). When the wGRS was divided into quartiles, individuals in the top quartile had a 9.31 times increase risk of PBC relative to those in the first quartile. Certainly, as clinical sequencing becomes commonplace and predictive values improve, one can imagine the value of such risk scores as part of the diagnostic armamentarium in patients and at risk populations.

To date, GWAS efforts have focused on the identification of genetic variants associated with PBC itself, but not specific sub-phenotypes of disease such as treatment response and liver-related complications. The ability to identify patients who are potentially at risk of an accelerated natural history or complication of their disease based on their genetic architecture would certainly be a valuable clinical tool for risk stratification and prognostication. While efforts are underway to identify variants associated with outcomes such as response to therapy and disease progression in PBC, given the number of patients and events required to achieve adequate statistical power, multicenter international collaborative efforts will undoubtedly be required to obtain meaningful results.

Perhaps one of the most obvious opportunities for clinical translation of findings from GWAS studies is the identification of novel therapeutic targets. There is clearly a clinical need in PBC given that UDCA is the only approved therapy, and for unknown reasons, a significant proportion of patients fail to respond to treatment[4]. As mentioned, the IL-12 pathway has been strongly implicated in the pathogenesis of PBC as well as other

autoimmune diseases. The monoclonal antibody ustekinumab targets the IL-12 p40 subunit and thus, exerts its effect on both the IL-12/T_H1 and IL-23/T_H17 axes. While ustekinumab has demonstrated therapeutic benefit in patients with Crohn's disease[78] and psoriasis[79], pilot studies in patients with PBC have been disappointing, with no patients achieving the predefined primary endpoint of biochemical response in a recently reported Phase II study (NCT01389973). Accumulating evidence suggests that co-inhibitory molecules are key in the prevention of autoimmune disease[80]. CTLA-4 is a co-inhibitor that suppresses T cell activation through binding to CD80 and CD86 on APCs with higher affinity than its co-stimulatory counterpart CD28[81]. CTLA-4 was a main focus of many candidate gene studies of PBC, but never demonstrated association at genome-wide significance; though interestingly, variants at the *CD80* locus have been associated with PBC in GWAS efforts[41]. Abatacept, a fusion protein consisting of the extracellular domain for CTLA-4 and the constant region of IgG (CTLA-Ig)[82], has been developed and improves outcomes in patients with rheumatoid arthritis[83] and psoriasis[84]. Modulation and prevention of T cell priming via this pathway could have therapeutic implications in PBC and in fact pilot studies are underway to assess its efficacy in patients with poor response to UDCA (NCT02078882).

TNF-α is an activating factor for a number of intracellular pathways and plays an important role in liver homeostasis[85]. GWAS in PBC have identified several loci containing genes in the TNF-α signaling pathway including *TNFRSF1A*, *DENND15*, and *TNFAIP2*[41,42] and pathway-based analysis has indicated that TNF signaling may underlie the genetic predisposition of PBC[46]. Whether anti-TNF-α agents, which have clearly been effective in other autoimmune diseases such as CD, UC, and RA, will have a therapeutic role in selected subsets of PBC patients remains to be seen.

Though T lymphocytes seem to be the primary mediators of damage in PBC, the presence of disease specific antibodies in the vast majority of patients suggests a role for B cells as well. Several variants at loci associated with B cell function have been identified in GWAS. For example, *POU2AF1* and *IKZF3* encode transcription factors important in B cell maturation and the development of long term immunity[86,87], SPI-B is a mediator of B cell signaling[88], and IL-7R participates in pre-B cell expansion[89]. Selective depletion of B cells with the anti-CD20 antibody Rituximab was associated with biochemical improvement in a pilot study of PBC patients who were non-responders to UDCA[90] (NCT00364819), though some safety concerns have been raised after mouse models demonstrated disease exacerbation following anti-CD20 therapy[91]. In sum, the biological pathways implicated in PBC through GWAS have provided a ripe landscape for exploration of alternative therapeutic options. However, a greater appreciation of the functional relevance of observed associations to each pathway will be crucial to successful application of targeted therapies in PBC.

CONCLUSIONS

Significant advancements have been made in our understanding of human genetics over the last decade and progress continues at a seemingly exponential pace. GWAS have been a critical stepping stone in the hunt for genetic variants contributing to PBC pathogenesis, particularly in identifying genes outside the HLA locus that might be involved in disease. However, it has become evident that the genes thus far implicated in PBC modulate non-

specific immunologic pathways important in many different autoimmune diseases, rather than conferring organ specific risk. Given the number of shared risk loci among autoimmune diseases in general, it seems likely that a mosaic of genetic variations contribute to disease specificity, rather than true disease-specific associations. Certainly, the role of rare genetic variation and other structural and non-structural genetic changes, environmental influences, and interactions between the two in conferring disease specificity remain to be defined. Importantly, before meaningful clinical translation is realized, functional consequences of identified variants at the level of the end organ need to be understood. This will be especially important for therapeutics so that novel interventions can be disease specific rather than having systemic effects akin to the pleiotropic genes thus far identified.

Acknowledgments

This work was supported by a grant to Dr. Konstantinos N. Lazaridis from the National Institutes of Health (R01 DK80670).

Abbreviations

AMA	anti-mitochondrial antibody
APC	antigen presenting cell
CD	Crohn's Disease
dnTGFBR2	dominant negative TGFβ receptor 2
FDR	first degree relative
GWAS	genome wide association study
HLA	human leukocyte antigen
IFN-γ	interferon gamma
MHC	major histocompatibility complex
MS	multiple sclerosis
NF-κB	nuclear factor kappa beta
PBC	primary biliary cirrhosis
PDC	pyruvate dehydrogenase complex
RA	rheumatoid arthritis
SLE	systemic lupus erythematosis
SNP	single nucleotide polymorphism
T1DM	Type 1 diabetes mellitus
T_H1	T-helper 1
T_H17	T-helper 17
TNF	tumor necrosis factor

UC	ulcerative colitis
UDCA	ursodeoxycholic acid

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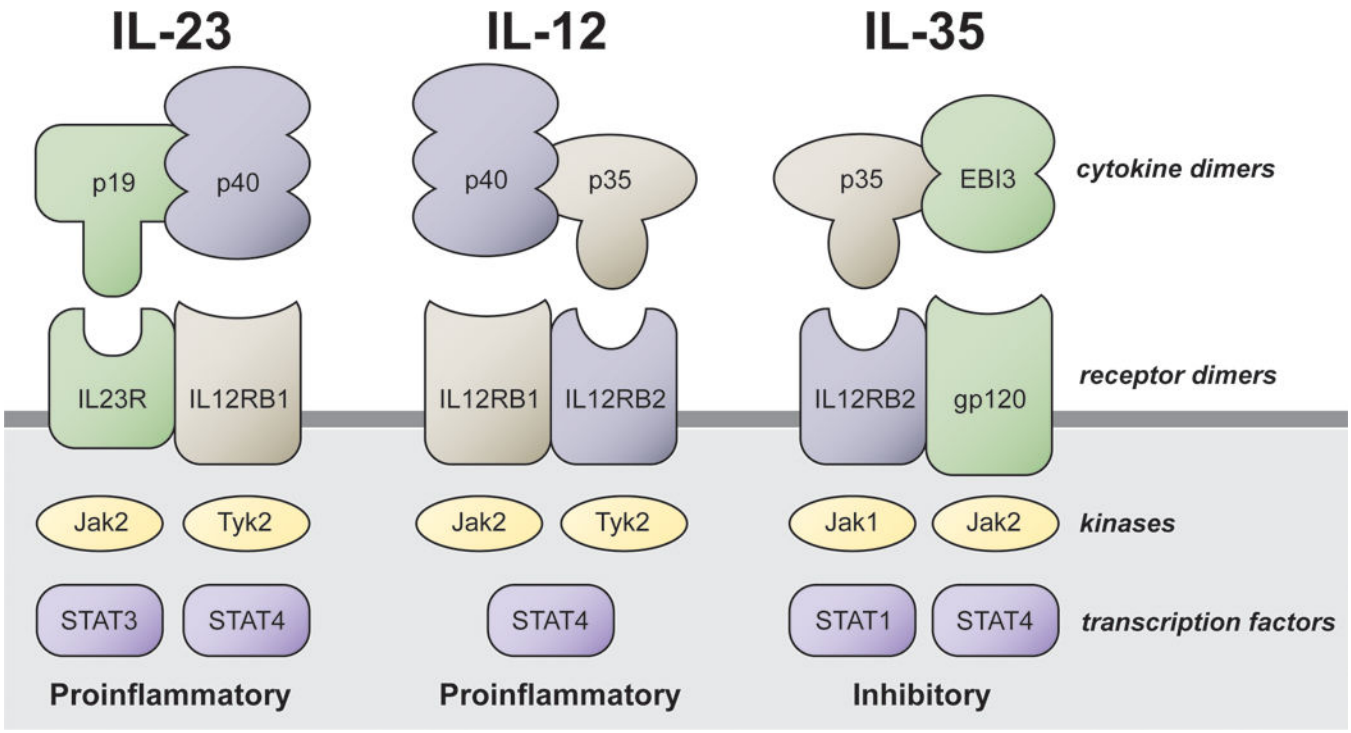

Figure 1.

Chain-sharing between IL-12 and other members of the IL-12 cytokine family. Protein units comprising the dimeric cytokines and receptors, as well as the key downstream kinases and transcription factors, are shown for the proinflammatory IL-12 family members IL-23 and IL-12 and the inhibitory IL-12 family member IL-35. IL-12, the key cytokine in T_H1 immune polarization, shares the IL-12 p40 and IL-12 receptor β1 subunits with T_H17 polarizing IL-23 as well as the IL-12 p35 and IL-12 receptor β2 subunits with inhibitory IL-35. GWAS in PBC has identified associations with the genes encoding IL-12 p35 (*IL12A*) and IL-12 receptor β2 (*IL12RB2*), as well as with *TYK2* and *STAT4*.

Table 1

Non-HLA risk loci identified through GWAS as associated with PBC at genome wide level of significance

Study	Platform	Cases (n)	Controls (n)	Locus	SNP	Associated Genes	OR (95% CI)	p-value
Hirschfield *et al.*	Illumina HumanHap370	1031	2713	1p31	rs3790567	IL12RB2	1.51 (1.33–1.70)	2.76 × 10–11
				3q25	rs6441286	IL12A	1.54 (1.38–1.72)	2.42 × 10–14
Liu *et al.*	Illumina 610K	945	4651	7q32	rs10488631	IRF5-TNPO3	1.57 (1.38–1.77)	8.66 × 10–13
				17q12	rs9303277	IKZF3, ORMDL3	1.38	1.69 × 10–9
				19q13	rs3745516	SPIB	1.46	7.97 × 10–11
Mells *et al*.	Illumina 660W-Quad	1840	5163	1q31	rs12134279	DENND1B	1.34 (1.25 – 1.45)	2.06×10–14
				2q32	rs10931468	STAT4, STAT1	1.50 (1.37 – 1.64)	2.35×10–19
				3q13	rs2293370	CD80	1.35 (1.23 – 1.47)	2.53×10–11
				3p24	rs1372072	PLCL2	1.20 (1.12–1.27)	2.28×10–8
				4q24	rs7665090	NFKB1	1.26 (1.18 – 1.34)	4.06×10–12
				5p13	rs860413	IL7R	1.30 (1.21 – 1.40)	1.02×10–11
				7p14	rs6974491	ELMO1	1.25 (1.16 – 1.36)	4.44×10–8
				11q13	rs538147	RPS6KA4	1.23 (1.15–1.31)	2.06×10–10
				11q23	rs6421571	CXCR5, DDX6	1.37 (1.25 – 1.50)	2.69×10–12
				12p13	rs1800693	TNFRSF1A	1.22 (1.14 – 1.30)	1.80×10–9
				14q24	rs911263	RAD51B	1.29 (1.20 – 1.39)	1.76×10–11
				14q32	rs8017161	TNFAIP2	1.22 (1.16–1.27)	2.61 × 10–13
				16p13	rs12924729	CLEC16A, SOCS1	1.29 (1.20 – 1.38)	2.95×10–12
				16q24	rs11117432	IRF8	1.31 (1.21 – 1.43)	4.66×10–11
				22q13	rs968451	TAB1, SYNGR1	1.27 (1.18 – 1.38)	1.08×10–9
Nakamura *et al.*	Affymetrix Axiom	1274	1091	9q32	rs4979462	TNFSF15	1.56 (1.39–1.76)	2.84 × 10–14
				11q23	rs4938534	POU2AF1	1.39 (1.24–1.56)	2.38 × 10–8
Juran *et al.*	Immunochip	2426	5731	13q14	rs3862738	TNFSF11	1.33 (1.20 – 1.47)	2.18×10–8
Liu *et al.*	Immunochip	2861	8514	12q24	rs11065979	SH2B3	1.27 (1.19–1.34)	1.18×10–14
				17q21	rs17564829	MAPT	1.25 (1.16–1.35)	2.15×10–9
				19p12	rs34536443	TYK2	1.29 (1.21–1.38)	1.29×10–13

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Study	Platform	Cases (n)	Controls (n)	Locus	SNP	Associated Genes	OR (95% CI)	p-value
Hirschfield *et al.* *	Illumina HumanHap370	1351	4700	1p36	rs3748816	MMEL1	1.33 (1.20–1.47)	3.15×10^{-8}

* replication study of suggestive SNPs from previous GWAS in larger cohort

Table 2

Genes associated with PBC and other autoimmune diseases and their corresponding function.

PBC Associated Genes	General Function	Diseases with Shared Risk Loci
IL12RB2	T cell differentiation	Behcet's
IL12A	T cell differentiation	Celiac
IRF5-TNPO3	immune system activation	UC, RA, SLE, SSc
IKZF3, ORMDL3	B cell proliferation and differentiation	UC, CD, RA, T1DM
SPIB	lymphoid specific enhancer, B cell signalling	n/a
DENND1B	clathrin mediated endocytosis	CD
STAT4, STAT1	IL-12 signalling, T helper cell differentiation	Celiac, RA, SLE, SSc, Sjogren's, Behcet's, IBD
CD80	T cell costimulatory signal	MS, celiac, vitiligo, SLE
PLCL2	signal transduction	RA
NFKB1	transcription regulation, involved in immune activation	UC
IL7R	lymphocyte development	MS, UC
ELMO1	phagocytosis and cell migration	Celiac, RA
RPS6KA4	regulator of inflammatory genes	IBD
CXCR5, DDX6	B cell migration and/or differentiation	Celiac, vitiligo, RA, IBD
TNFRSF1A	regulatory of inflammation	MS
RAD51B	DNA repair	RA
TNFAIP2	mediator of inflammation	n/a
CLEC16A, SOCS1	negative regulation of cytokine signalling via JAK/STAT	MS, UC, T1DM
IRF8	negative regulation of type I IFN stimulated genes	MS, IBD, RA, SSc
TAB1, SYNGR1	mediates intracellular signaling	RA
TNFSF15	mediates activation of NFKB and promotes apoptosis	UC, CD
POU2AF1	essential for B cell response to antigens	n/a
TNFSF11	T cell regulation and bone resorption	CD
SH2B3	negative regulator of cytokine signalling	Celiac, RA, T1DM, Vitiligo, hypothyroidism
MAPT	maintenance of neuronal polarity	n/a
TYK2	mediates intracellular signaling	IBD, RA, SLE, psoriasis, T1DM
MMEL1	metalloproteinase involved in embryonic development	MS