Autoimmun Highlights (2012) 3:1–9
DOI 10.1007/s13317-011-0023-y

REVIEW ARTICLE

Towards systemic sclerosis and away from primary biliary cirrhosis: the case of PTPN22

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Received: 16 July 2011 / Accepted: 29 July 2011 / Published online: 7 September 2011

Abstract Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease characterized by immune-mediated destruction of the small and medium size intrahepatic bile ducts. PBC patients often have concomitant autoimmune diseases, which are most often autoimmune thyroid disease, as well as Sicca syndrome. Occasionally, some PBC patients will also have systemic sclerosis of the limited cutaneous type (lcSSc). Conversely, up to one-fourth of SSc patients are positive for antimitochondrial antibody, the serologic hallmark of PBC. It is also common for SSc patients to have concomitant autoimmune disease, which may include PBC in rare cases. This has led to speculation of shared environmental and/or genetic factors, which lead to the development of PBC in SSc patients and vice versa. Recent genetic studies have revealed associations with several genes in both SSc and PBC. PTPN22 is one gene that has been associated with SSc, but not with PBC. It may be argued that some SSc patients with a particular genotype, which shares genes found in both conditions may develop PBC. Likewise, particular genes such as PTPN22 may infer susceptibility to SSc alone. The presence of PTPN22 may also contribute to the development of SSc in PBC patients. The lack of a large number of overlapping genes may, in part, explain the relative rarity of PBC with SSc and vice versa. This review will examine the literature surrounding the genetic associations of PBC and SSc, and the role of PTPN22 in particular.

Keywords Autoimmunity · Autoimmune disease · Bile ducts · Cholestasis · Liver · Immunology · Rheumatology

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Introduction

Primary biliary cirrhosis (PBC) is a chronic cholestatic liver disease characterized by immune-mediated destruction of the small- and medium-sized bile ducts [1–3]. The prevalence of PBC ranges from 28 to 402 per million. PBC predominantly affects middle-aged women [4]. Recent studies indicate that the prevalence of PBC is rising [4–7]. The autoimmune pathogenesis of PBC is supported by a plethora of experimental and clinical data, such as the presence of autoreactive T cells in PBC patients, and serum autoantibodies characteristic of the disease [8–20].

High-titer serum antimitochondrial autoantibodies (AMA) are pathognomonic for PBC, being present in 90–95% of patients [1–3, 8, 19, 21–28], and seropositivity

of AMA in asymptomatic patients is predictive of eventual disease development [4]. These autoantibodies are specific to the lipoylated domains within components of the 2-oxoacid dehydrogenase family of enzymes, particularly the E2 component of the pyruvate dehydrogenase complex (PDC-E2) [1–3, 8, 21–24, 28–31]. In addition to AMA, PBC-specific anti-nuclear autoantibodies (ANA) are present in approximately 30% of patients [21, 22, 24, 26, 28–30, 32, 33]. There are several PBC-specific ANA patterns detected by indirect immunofluorescence, including the "multiple nuclear dot" and "nuclear membrane/rim" patterns [21, 29, 30, 32, 34]. In most cases, the "multiple nuclear dot" pattern corresponds to autoantibodies against Sp100, Sp140, promyelocytic leukaemia nuclear body proteins, and small ubiquitin-like modifiers [5, 21, 33, 35–43]. The "nuclear envelope/rim" pattern corresponds to reactivities specific for gp210 and nucleoporin p62 [32, 33]. Up to 30% of PBC patients have both patterns, which demonstrate significant disease specificity. The recognition of these patterns is not easy, and may be confused with similar pattern. ANA may be present in PBC patients who are found to be AMA negative, in addition to asymptomatic individuals and family members of PBC patients [5, 21, 39–42, 44, 45].

The aetiology of PBC is unknown, however, it is believed that genetic susceptibility, and environmental factors are involved in concert [46–50]. A number of xenobiotics and infectious agents have been proposed to induce the disease in individuals who are genetically predisposed [46–50]. Studies in animal models of the disease have provided data to suggest that specific infectious and environmental triggers can induce PBC-specific pathological features, probably by the mechanism of molecular mimicry [36, 46, 51–62]. This mechanism implies that microbial sequences mimicking self proteins are capable of inducing an immune response, which cross reacts with autoantigens inducing autoimmunity, and overt autoimmune disease [63–71]. This would occur in the setting of T regulatory impairment, particularly in susceptible individuals [72–77]. Presenting symptoms may include non-specific symptoms such as pruritus and/or fatigue [2, 3]. In more severe cases, the patients may present with jaundice and portal hypertension [2, 3]. Most are asymptomatic and diagnosed incidentally during assessment for pruritus, fatigue or other extrahepatic conditions (commonly other autoimmune diseases), or during screening when a close family member is diagnosed with PBC [78, 79]. A diagnosis of PBC is made if two of the following three criteria are fulfilled: elevated alkaline phosphatase (ALP), the presence of serum AMA (titre $\geq$1:40), and characteristic liver histology [2, 3, 80]. Serum AMA may precede the onset of symptoms and/or biochemical evidence of disease by several years, and prospective studies suggest that AMA-positive asymptomatic patients go on to develop PBC [4].

Primary biliary cirrhosis progresses over many decades, with an unpredictable progression pattern from patient to patient. In most of the cases, the disease progresses in a slow pace, but in minority the disease is rapidly progressive, leading to cirrhosis and liver failure within a few years. Some studies suggested that patients with PBC-specific ANA may progress faster than those without these autoantibodies [5, 21, 33, 35–41, 81, 82]. The introduction of medical treatment with ursodeoxycholic acid (UDCA) has greatly improved the life expectancy and quality of life of PBC patients. When UDCA is administered in early PBC at adequate doses (13–15 mg/kg/day), the disease progression is often altered, with many patients having a normal life expectancy [83, 84]. Patients at the very end stages of the disease require liver transplantation [85]. Like other conditions of presumed autoimmune origin, the disease may re-occur several years after transplantation [86].

Concomitant autoimmune diseases are often found in patients with PBC [1–3] and 30–70% of the patients have *Sicca* symptomatology, with or without formally diagnosed Sjögrens syndrome, as well as autoimmune thyroiditis [78, 87–89]. However, a small number of patients also have concomitant systemic sclerosis (SSc) [78, 87–89]. Additionally, PBC is the most common autoimmune liver disorder in SSc patients [78, 87–89]. Several factors may be involved which induce a small number of PBC patients to develop SSc, including environmental and genetic causes. This review will examine the genetic background behind PBC and SSc, and highlight those genes which are common to both diseases, as well as those which are exclusively present in each. Some genes serve as an example of how susceptibility can be inferred in one disease, while being protective in another. This raises the possibility that although several genes are important for the development of PBC, only a small number are involved in the pathogenesis of both PBC and SSc.

Systemic sclerosis

Systemic sclerosis is a systemic connective tissue disease characterized by vascular and immune dysfunction, with features of skin sclerosis and a potential involvement of other organs (kidney, esophagus, heart and lung are the most frequent targets). Liver involvement is relatively rare. The prevalence of scleroderma ranges from 50 to 200 per million, with a higher female preponderance [90, 91]. Clustering within families is observed, and the high frequency of other autoimmune disorders in families of patients with scleroderma suggests genetic involvement. In addition, infectious agents have been suggested as possible

contributing factors in the development and progression of SSc, through the mechanism of molecular mimicry [92–94].

Autoantibodies associated with the limited cutaneous form of SSc include anticentromere antibody (ACA), anti-Th/To, anti-U1-RNP, and PM/Scl [95]. The diffuse cutaneous form of SSc is characterized by topoisomerase I antibody (ATA, also known as anti-Scl-70), anti-RNA polymerase III and anti-U3-RNP [95]. ATA has been associated with severe lung disease in the diffuse form of SSc [95].

PBC in SSc and SSc in PBC

PBC is known to occur in a small number of patients with SSc [96], however, liver disease is not a significant feature of scleroderma, with liver disease being present in a higher proportion of controls in large studies [97, 98]. The association of SSc and PBC was first described in the context of PBC and limited scleroderma [99], which was followed by further case reports [100, 101]. The prevalence of clinically evident PBC was 2% in a series of 817 patients with SSc [102].

Two large cohorts of PBC patients estimated the prevalence of SSc in PBC to be approximately 8% [103]. However, case reports [5, 51, 99–101, 104–112] and some series reported a prevalence of 3–50% [96, 103, 105, 111, 113, 114]. Epidemiological studies on PBC note a small number of patients who also have SSc or scleroderma. One study found scleroderma in 1% of a cohort of French PBC patients, with 1% of their first degree relatives and 1% of controls also having scleroderma [87]. An American study found that 2% of PBC patients and 1% of their first degree relatives had scleroderma, which was found in none of the controls [78]. First degree relatives with scleroderma were more often sisters, followed by daughters [78, 88].

Genetics of PBC

As mentioned, there is an increased risk of developing PBC, as well as other autoimmune diseases, if a first degree relative is affected by the disease [78, 87–89]. This, and recent twin studies are suggestive of genetic influences which predispose an individual to not only PBC, but also to autoimmune disease. Twin studies have especially demonstrated the role of genetics in PBC [115]. Sixteen pairs of PBC twins were identified from a 1,400 family cohort from several worldwide centers, with eight MZ and eight DZ pairs [115]. Five of eight MZ pairs were concordant for PBC (63%), all of which were female [115]. This reflects one of the highest concordance rates among all autoimmune disease where twin studies have been preformed. In support for the role of genetic factors in PBC are also the reported defects in sex chromosomes [116–118].

The genome wide association study (GWAS) has been instrumental in the understanding of the genetic basis of autoimmune disease [96]. In recent years, GWAS studies in PBC have implicated a number of genes as being associated with the disease [119, 120]. Before GWAS, several HLA haplotypes were identified among pairs of PBC patients or small clusters, however until recently the only common HLA haplotype seen widely was HLA-DR8 [13, 120, 121]. Tsuji and colleagues [38] identified HLA-DR8 in 29.4% of PBC patients [121] and Invernizzi reported that HLA-DR8 is associated with PBC in Italian cohorts [122]. Both Invernizzi et al. and Donaldson and colleagues have reported that HLA-DR11 confers protection from PBC in studies involving cohorts of Italian patients, but the former study was unable to identify HLA-DR11 as been negatively associated with PBC in a cohort from the UK [121, 122]. HLA-DR13 was found to be protective in both populations [120–122]. A GWAS carried out by Hirschfield et al. [123] involving 536 PBC patients and 1,536 controls from Canada and USA, found associations with HLA and non-HLA loci. The strongest HLA association was with HLA DQB1 [123]. Non-HLA loci included two single-nucleotide polymorphisms (SNPs) at IL12A loci, and one SNP at the IL12RB2 locus [123]. Associations were also found with STAT4 and CTLA4, which have also been associated with rheumatoid arthritis and systemic lupus erythematosus, as well as other autoimmune diseases [124]. Similar findings were reported with IL12A and IL12RB in an Italian cohort [125]. Additionally, associations were made with HLA regions DRB1, DQA1, DQB1, and DQA2, as well as non-HLA regions such as IRF5, SPIB, and the IKZF3-ORMDL3 of chromosome 17q12-21 [125].

The identification of STAT4 is significant, as it is involved with IL12 signalling, and has been linked with other autoimmune diseases [125]. Although no association has been found between STAT4 and the autoimmune disease commonly found along with PBC, it is of interest given its association with SSc (see below). Hirschfield et al. [126] have also identified associations with variants at IRF5-TNPO3, 17q12-21, and MMEL1. The most recent genetic study was carried out on a UK population of 1,840 PBC cases, and 5,163 controls [127]. That study confirmed previous associations with MMEL1, IL12RB2, IL12A, IRF5, ORMDL3, SPIB, and several MHC [127]. New associations were found with 12 other genes, including STAT4 [127]. In another study involving a cohort of Japanese PBC patients and controls, no association was found with IL12A, IRF5 or SPIB [128]. However, that study did find an association between PBC and 17q12-21 [128]. The same group of investigators went on to investigate whether

the Fc receptor-like 3 (FCRL3) was associated with PBC in Japanese and Italian cohorts, as it has been found to be associated with several other autoimmune disease, especially in Japanese patients [129]. A significant association between FCRL3 and PBC was found in Japanese but not in Italian patients [129].

Although these studies provide us with (usually positive) associations, they do not give us insight as to whether susceptibility to specific genes is associated with disease severity. Thus, it is not clear as to whether the possession of an individual gene or multiple genes infers susceptibility to a more advanced, or aggressive form of the disease, or whether these genes can predict an unfavorable outcome over the course of the disease. As well, the presence of susceptibility genes may be predetermined by geographical location or origin/ethnicity (see below).

Genetics of SSc

Genome wide association studies have also contributed to the identification of several genes associated with SSc [130, 131]. Among Caucasian and Hispanic SSc patients, positive HLA associations include HLA-DRB1*1104, DQA1*0501, DQB1*0301, with negative associations in those groups being DRB1*0701, DQA1*0201, DQB1*0202, and DRB1*1501 [132]. Positive associations among African Americans have been found with HLA-DRB1*0804, DQA1*0501, and DQB1*0301 [132]. ACA positivity has been closely associated with HLA-DQB1*0501 [132], and ATA positivity has been associated with HLA-DRB1*1104 [132]. Non-HLA regions have also been identified in SSc, and include STAT4 [102, 131, 133–135], IRF5 [122, 131, 136], BANK1 [132, 137], TNSF4 [132], TBX21 [102], IL-23R [102], and C8orf13-BLK [132] among others [131]. Two studies have also identified an interesting gene, PTPN22, with SSc in large cohorts of American and European patients [138, 139]. PTPN22 is of interest given its link with other autoimmune diseases (see below).

Common genes in PBC and SSc

Genes which have been identified in both PBC and SSc include STAT4 and IRF5 (Table 1). This raises the possibility that these genes are involved in the development of SSc in PBC patients, or PBC in SSc patients. As SSc in PBC is relatively uncommon, one would expect a low prevalence of STAT4 and/or IRF5 in PBC patients, and indeed, only weak associations have been made with STAT4 in PBC [124]. As well, STAT4 has been associated with ACA positivity in SSc patients [102, 132, 139]. This is of interest as a study by Akimoto and colleagues found that

Table 1 Positive and negative genes in primary biliary cirrhosis (PBC) and systemic sclerosis (SSc)

Gene	Primary biliary cirrhosis	Systemic sclerosis
HLA		
DR8	+	−
DR11	−	+
DQB1	+	+
DRB1	+	+
DQA2	+	−
DQA1	+	+
Non-HLA		
IRF5	+*	+
STAT4	+	+
PTPN22	−	+
SPIB	+*	−
BANK1	−	+
IL12A	+*	−
IL12RB	+	−
MMEL1	+	−
IL-23R	−	+
TNSF4	−	+
CXCR5	+	−
NKFB1	+	−

The major positive and negative genetic associations found for HLA and non-HLA genes identified in PBC and SSc are presented in simplified form. In a shared gene hypothesis, individuals with genetic characteristics shared between the two diseases, maybe at risk of developing one disease in addition to the other (such as STAT4). Likewise, certain genes infer susceptibility to only one disease in isolation (such as PTPN22 in SSc). As well, some genes may be positively associated with one disease, but protective against another disease (such as DR11 in PBC)

* No association found in Japanese patients: note that no consensus between studies has been reached for all genes and the most representative associations (positive or negative) are presented

80% of PBC-SSc and 100% of PBC-SSc spectrum (not fulfilling the criteria for full PBC-SSc) were ACA-positive, compared to only 25% of PBC patients without SSc [5]. It would be of interest to see whether STAT4 is a feature found in the few PBC patients who develop SSc, and vice versa. What role IRF5 may play is unclear, as it is more commonly associated with the diffuse form of SSc, and PBC-SSc is usually found in patients with the limited form of the disease. The small number of overlapping genes may explain the relative rarity of SSc in PBC and vice versa.

PTPN22: towards SSc and away from PBC

PTPN22 encodes an 807-amino acid residue found in haematopoietic stem cells [140, 141]. Of relevance to the

pathogenesis of SSc, PTPN22 is involved in T and B cell signaling, and has been associated with ATA positivity in Caucasian patients [130, 139]. PTPN22 has been linked with altered T and B cell function, including decreased CD4+ T and B cell activation, and a shift in memory T and B cell populations [142, 143]. The presence of PTPN22 in association with SSc is not surprising, given that it has been implicated in multiple other autoimmune diseases. Associations with PTPN22 have been made with rheumatoid arthritis [140, 144, 145], juvenile idiopathic arthritis [146, 147], systemic lupus erythematosus [148, 149], autoimmune thyroid disease [27, 150, 151], myasthenia gravis [152], vitiligo [153], Addison's disease [154], and alopecia areata [155].

Given that PTPN22 has been associated with other autoimmune associations, a study speculated that this gene may confer susceptibility to PBC [156]. These investigators have studied a Canadian cohort of 160 Caucasian PBC, all AMA-positive, which were genotyped for the PTPN22 (C1858T) SNP, and they compared their results with those obtained in 290 demographically matched, healthy controls [156]. No association was found between the PTPN22 (1858T) allele and PBC, with a frequency of 7.5% in PBC patients compared to 8.4% in the controls [156]. There was also no significant association between PTPN22 and PBC patients with concomitant autoimmune disease [156]. Of note, 10 patients (6% of the cohort) had concomitant scleroderma, but it is unknown as to whether these patients were among the small group of patients with the PTPN22 (1858T) allele.

Given the geographical differences seen in terms of how some genes function [121, 122, 128, 129], it may be the case that these differences relate to the prevalence of autoimmune disease in particular geographical locations. PBC, as well as other autoimmune disease, have been found to have higher prevalence rates in countries with more northern latitudes, such as the UK and Finland [4–7]. The studies by the groups of Donaldson and Invernizzi [121, 122] have shown that protective genes for PBC are more prevalent among Italians (southern latitude), compared to their more northern neighbors in the UK. As well, differences in associated genes have been found between Japanese and Italian cohorts [128, 129]. The prevalence of disease associated genes in relation to geographical location is not currently well defined. As PTPN22 is associated with multiple autoimmune diseases, it could be argued that the prevalence of PTPN22 may be increased in regions where there is a high rate of autoimmune diseases, including PBC. These differences may be present both geographically, as well as ethnically. Indeed, PTPN22 has been found to be more frequent in northern countries, with a gradual decrease in frequency with decreasing latitude [157]. Finland and Ukraine have the highest PTPN22 frequencies at 15 and 14.1%, respectively [157]. Moving more south, the frequency in France and Spain is approximately 7%, and lowest in Italy with a frequency of 2% [157]. Begovich and colleagues [140] note that PTPN22 is virtually absent in African and Asian populations, but has a frequency of 6–9% in American and Australian Caucasians with European ancestry. This distribution rate may also play a role in the regulation of susceptibility to certain infectious agents, some of which may be implicated in the pathogenesis of autoimmune disease, including PBC and SSc [11, 158, 159].

A relationship with infection has also been indicated with PTPN22, which is of interest given theories surrounding infection and molecular mimicry in the pathogenesis of autoimmune diseases. A particular variant of PTPN22, R620W, has been suggested to be protective against tuberculosis infection [134, 160–162]. However, PTPN22 has been found to increase susceptibility to infection by invasive bacteria such as pneumococcus [163]. Further characterization of the relationship between PTPN22 and infection may provide some clues as to the link between autoimmune disease and infectious agent.

Conclusions

The GWAS has provided numerous genes to be associated with PBC and SSc, a number of which are found in both conditions. This raises the question as to whether these shared genes are involved in the pathogenesis of SSc in PBC patients, or PBC in SSc patients. It may be argued that implicated genes, which do overlap between the two conditions, are responsible, or at least play a role, in the development of each disease in isolation. For example, PTPN22 has been associated with the development of SSc and other autoimmune diseases but not PBC. If an individual had a particular PTPN22 disease-associated allele (in addition to other SSc-specific genes) along with the appropriate environment, than that individual may develop SSc in isolation, or with concomitant autoimmune disease associated with PBC. That individual would likely not develop PBC. If, however, that individual also had alleles such as STAT4 (or others associated with PBC, or PBC and SSc), then that individual may develop PBC, given the appropriate environmental stimuli.

It is likely that further genetic associations will demonstrate a link between PBC, and autoimmune disease that PBC is associated with. As well, associations may also account for the fact that family members of PBC patients also have a higher frequency of PBC and other autoimmune disease. In addition to genetic factors, common environmental factors such as pathogens may also be shared between PBC and SSc, which may also contribute to

the development of PBC-SSc in genetically susceptible individuals.

Conflict of interest None of the authors has a conflict of interest to declare.

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