Primary biliary cirrhosis (PBC) is an autoimmune chronic cholestatic liver disease characterized by immune-mediated injury of small and medium-sized bile ducts, eventually leading to liver cirrhosis. Several studies have addressed PBC immunopathology, and the data support an immune activation leading to autoantibodies and autoreactive T cells acting against the lipoylated 2-oxoacid dehydrogenase complexes. The causes of the disease remain unknown, but environmental factors and genetic susceptibility both contribute to its onset. Over the past two decades several association studies have addressed the role of genetic polymorphisms in PBC pathogenesis and have reported multiple associations. However, only a few studies had sufficient statistical power, and in most cases results were not independently validated. A genome-wide association study has recently been reported, but this too awaits independent confirmation. The aim of this present work is to critically review the numerous studies dedicated to revealing genetic associations in PBC, and to predict the potential for future studies based on these data.

PBC is characterized by the presence of antimitochondrial antibodies (AMAs) - which are present in 90 to 95% of patients and are often detectable years before clinical signs appear [2]; high plasma levels of immunoglobulin M (IgM) [3]; and high-titer antibodies against nuclear antigens (ANAs). It is estimated that 30 to 50% of patients also have specific ANAs, including antibodies to nucleoporin p62 (Nup62), a glycoprotein located within the nuclear pore complex (NPC) [4]. These antibodies are associated with more severe forms of the disease. While AMA presence is often used for diagnostic purposes, ANAs and Nup62 could be linked to prognosis and are helpful tools in the management of patients with PBC, particularly in the AMA-negative subgroup [5,6].

PBC primarily affects middle-aged women, with a female/male ratio of 9/1, a characteristic shared by other autoimmune diseases [7]. It also seems to be more common among the first-degree relatives of patients [8,9]. Studies of the annual incidence and prevalence of PBC in different geographical areas suggest the impact of ethnic influences, environmental factors and the non-uniform criteria used for the diagnosis of PBC. PBC still appears to be more frequent in northern Europe and the United States, but overall the incidence ranges between 0.7 and 49 per million population, while the prevalence is between 6.7 and 402 cases per million population [10], thus making PBC a rare disease according to the 2002 Rare Disease Act. Several studies have reported a substantial increase in PBC prevalence and incidence over recent decades, similar to other autoimmune diseases [11]. This is mostly due to a better and earlier recognition of disease, and to more sensitive diagnostic procedures [12]. PBC is now diagnosed at an earlier stage in its clinical course than it was in the past, with 50 to 60% of patients asymptomatic at diagnosis, and one-third of them remaining symptom free for many years.

The diagnosis of PBC is currently based on three criteria: serological positivity for AMA, a cholestatic biochemical picture with elevated levels of serum alkaline phosphatase and γ glutamyl transferase lasting for over 6 months, and histological features compatible with the presence of the disease. A probable diagnosis requires the presence of two of these three criteria, and a definite
diagnosis requires all three. In about 5 to 10% of cases, a compatible liver biopsy together with biochemical cholestatic features of PBC but in the absence of AMA is seen. This connotes the condition known as AMA-negative PBC or ‘autoimmune cholangiopathy’, now considered a nosological entity, practically identical to PBC apart from the serological profile [13,14]. From a clinical standpoint, PBC can be divided into four stages: pre-symptomatic (characterized by AMA seropositivity with abnormal liver tests and without symptoms), asymptomatic (AMA seropositivity and abnormal liver tests), symptomatic (patients present PBC-related symptoms), and decompensated (symptoms and complications of end-stage liver disease).

The natural history of PBC is characteristically associated with important variations: while some patients present with a slowly progressive disease, others have an early onset of complications. A recent case-control study [15] showed not only that PBC is associated with other autoimmune diseases in 30% of cases (Raynaud’s syndrome in 12%, Sjögren syndrome in 10%, rheumatoid arthritis in 10%, autoimmune thyroid disease in 9%, systemic lupus erythematosus (SLE) in 3% and scleroderma in 2% of cases), but also that this association may be considered a negative prognostic factor. Finally, although several studies have suggested that the early use of ursodeoxycholic acid has a positive impact on prognosis, none of the current models of treatment have shown a definitive impact on the natural history of PBC [16], and at the end stage of the disease, liver transplantation is the only effective mode of treatment [17].

**Etiopathogenesis of PBC**

Factors leading to PBC onset remain poorly understood, but several lines of evidence suggest that immune-mediated mechanisms play a crucial role. Numerous similarities exist between PBC and other autoimmune disorders, including female predominance, increased prevalence in subjects with a family history of PBC, and frequent coexistence with other autoimmune diseases. The tissue selectivity of the immune attack is particular to PBC, as is the poor responsiveness of patients to immune suppression. In addition, the breakdown of immune tolerance against mitochondrial and nuclear self-antigens is also unique to PBC.

Cholangiocytes play an important role in the pathogenesis of PBC and may account for the high tissue specificity. Indeed, the PBC paradox is that the damage is highly localized and only targets the lining of the small and medium-sized intrahepatic bile ducts, despite ubiquitous expression of the autoantigens [18]. The most recent data on apoptosis may provide the key to these observations [19]. Ultimately, the onset of PBC requires two components: a permissive genetic background and an environmental trigger. While the discussion of this latter aspect goes beyond the aims of the present article [20], we will now review the numerous studies that associate PBC onset with genetic variants and polymorphisms.

**Putative genomic associations in PBC**

PBC is more frequent in relatives of affected individuals, and the term ‘familial PBC’ has been coined to indicate families that have more than one case. Variable rates of familial PBC are seen in different geographical regions, possibly due to different methods of case definition. In general, data indicate that 1 to 6% of PBC cases have at least one other family member presenting with the disease [21]. Such familial prevalence rates are significantly higher than general population prevalence estimates, thus indicating a genetic predisposition to the disease. However, the difficulty of evaluating these data is that prevalence rates in the general population are still uncertain and control groups are not always included in family studies. The concordance rate observed among monozygotic twins for PBC is 63%, among the highest reported in autoimmune diseases. This reinforces the concept of an important genetic factor in susceptibility to this disease [21], but also highlights the necessity for an environmental insult, be it chemical, bacterial, or viral [22].

Several studies have attempted to identify the genes associated with PBC. No family study of genetic linkage has been performed, possibly because PBC is a relatively rare disease and it is therefore difficult to obtain DNA samples from a large number of representative families. All available studies were designed in a controlled cross-sectional fashion, but were prone to multiple sampling errors and biases caused by incorrect estimations. A multi-hit genetic model seems to apply to PBC, with different genetic variants conferring susceptibility (first hit) and others influencing disease progression (second hit). For this reason, most authors investigating genetic factors in PBC have studied their role in susceptibility to the disease (comparing allele and genotype frequencies in patients and controls), as well as in its severity (through the analysis of clinical characteristics of patients carrying different genotypes or alleles). No definitive association of PBC susceptibility or progression could be identified in these studies [23]. When an association was found, it has proved to be weak or limited to specific geographical regions. We note that this also applies to the study of the variants of major histocompatibility complex (MHC; including type I, II, and III loci), in which, unlike most autoimmune diseases, reported associations were often weak [24] or limited to specific geographical areas [25]. Similar findings were also reported from the study of the genetic variants of immunomodulatory molecules (such as chemokines, receptors), enzymes producing vasoactive
compounds, and bile-acid transporters [9]. The proposed associations are summarized next.

**Major histocompatibility complex and PBC**

Strong associations with specific MHC human leukocyte antigen (HLA) alleles have been reported in many autoimmune diseases, in some cases constituting the gold-standard for the diagnosis of otherwise undetermined cases [26].

Studies performed on small cohorts of subjects (between 21 and 75) have examined the association between HLA class I molecules and PBC susceptibility [27-33], but the conclusions of these early reports were affected by several major flaws, including limited statistical power, and technological problems for an accurate allele analysis. Nevertheless, our group reported that PBC is associated with various HLA-B alleles in a small proportion of patients [34]. It is possible that the positive association might be secondary to linkage disequilibrium. Based on the available data, we should therefore regard PBC associations with HLA class I genes as weak.

The association of HLA class II alleles with PBC has been widely studied in Caucasian and Asian patient cohorts. In studies from Germany, Spain, Sweden, and the United States, HLA-DRB1*08 (DRB1*08) was found with significantly higher frequency in patients with PBC compared to controls; cumulatively, data aggregation indicates that DRB1*08 might constitute a risk factor for PBC among Caucasians [32,35-38]. In 2001, data from Newcastle, UK demonstrated that the linkage of DQA1*0401 and DRB1*0402 is associated with PBC progression and not susceptibility [39]. Other studies in non-British European populations have not confirmed this association [30,33,34,40,41]. Moreover, other European studies suggested significant associations of PBC with DR3 [27,33] and DPB1*0301 [42], while the most recent study from the United States demonstrated an association between the DRB1*08-DQA1*0401-DQB1*04 haplotype and PBC, albeit in a minority of patients [38]. Finally, studies from Japan failed to provide a consistent picture of HLA class II associations with PBC [28,29,43]. Interestingly, in a large series of Italian patients with PBC and controls, we observed a protective effect of the DRB1*11 allele in PBC, which was later confirmed in a larger set of patients and controls along with a positive association with DRB1*08 [25].

In summary, we can conclude that the picture of HLA class II involvement in PBC is quite complex. We could assume that, similar to the epidemiological data, the genetic background in PBC could be associated with a geographical pattern.

Data from association studies of polymorphisms of tumor necrosis factor (TNF)-α in PBC are conflicting and a cautious interpretation is encouraged [44]. A polymorphism of the gene promoter region produces the more frequent variant TNF1, and the less frequent variant TNF2 [45], with TNF2 associated with increased transcription [46-48]. The prevalence of the TNF2 allele was reportedly protective against PBC onset [49] while two other studies independently failed to detect any difference in genotype distributions between patients and controls [50,51]. In the study from Tanaka and colleagues, heterozygous patients had a significantly worse prognosis compared to homozygous TNF1/TNF1 patients [50], as indicated by higher Mayo score value, currently the only validated index for PBC [52]. However, a study from Newcastle, UK did not confirm this alleged association [51]. Similarly, data obtained from Scottish, Brazilian, and Chinese patient cohorts with PBC [41,53,54], and from a small population of patients undergoing liver transplantation for end-stage PBC [55], revealed no association of TNF genotypes with disease susceptibility or onset.

High-throughput novel technologies have made the study of single nucleotide polymorphisms (SNPs) of candidate genes the method of choice for association studies in PBC. The analysis of SNPs can define the linkage of specific loci or neighboring regions with disease traits. We note that, in addition to the general considerations expressed above on the choice of candidate genes and populations, the study of SNPs should be more focused on coding variants (that is, with demonstrated effects on phenotype) of genes, although this might exclude other SNPs that are possibly in linkage disequilibrium with genes that are important for disease onset [56].

**Non-MHC genes in PBC**

Most studies of SNPs in PBC have been dedicated to molecules involved in regulating the immune response, thus hypothesizing that genomic differences at these levels might confer susceptibility to the loss of tolerance or to an aberrant immune response. Based on the expression of cytotoxic T lymphocyte antigen-4 (CTLA-4) by T cells following activation and the regulatory effect of this molecule on peripheral T cell responses, SNPs of CTLA-4 were suggested as factors facilitating the breakdown of tolerance. Accordingly, the coding 49A>G SNP was found associated with PBC in a large British study [57] and in 77 Chinese patients with PBC [58], while a smaller study from Brazil failed to confirm the association [41]. Several studies were further dedicated to SNPs of interleukins (ILs), based on their critical role in the regulation of the immune response. Prompted by experimental data such as its dysregulated production by monocytes in PBC [59], SNPs of IL-1 were studied. First, a study from the UK reported a significantly higher frequency of the IL-1B*1,1 genotype in patients with PBC compared to controls. The difference in the IL-1B*1,1
genotype distribution was even more marked in patients with early-stage disease, thus possibly indicating that \textit{IL-1} alleles might influence disease progression [39]. The lack of association with PBC onset was also independently confirmed by Hungarian [60] and Chinese [61] researchers. The latter group, however, more recently described an association of PBC with the \textit{IL1-RN} intron genotype, comparing frequencies in 77 patients with PBC and 160 controls [62]. Further, based on experimental evidence of cytokine profiles and their involvement in the development of T helper 1 cell responses, SNPs of the promoter region of the \textit{IL-10} gene were also analyzed in patients with PBC and controls [53,62,63]. Data from Italian and Japanese series demonstrated that both groups presented a higher prevalence of the -1082G/G genotype [63]. Such association was not confirmed in 77 Chinese patients with PBC [61,62].

SNPs of the 1,25-dihydroxyvitamin D receptor (\textit{VDR}) gene have been investigated in several studies, based on the dual role of vitamin D in the regulation of bone metabolism and inflammation. Accelerated bone loss rates in patients with prolonged cholestasis (as in PBC) have been repeatedly reported, sometimes with conflicting results, and in some cases with less than rigorous experimental designs. A significant association between \textit{BsmI} polymorphisms of \textit{VDR} and PBC was reported in patients with PBC from Germany, Hungary, and China [60,64-66], while the proposed association with bone loss [67] was not reproduced [68]. We believe that differences in the \textit{VDR} gene might unravel further potential scenarios to help explain the infrequency of PBC in African-American women [69], and could in turn support a possible role for sunlight exposure in PBC onset. Although fascinating, this assumption remains a hypothesis, yet to be confirmed.

Molecules responsible for bile acid transport and excretion in the biliary tree have been obvious targets in the search for genomic determinants of PBC onset. Interestingly, SNPs and mutation of ATP binding cassette (ABC) transporters involved in the secretion of bile from the hepatocyte [70] have been associated with intrahepatic cholestasis of pregnancy [71], somehow reproducing the clinical picture observed in PBC. Pauli-Magnus and colleagues [70] have carried out gene sequencing to investigate the variants of genes coding for the two main ABC transporters, identifying 45 \textit{ABCB11} and 46 \textit{ABCB4} variants, but found that no mutation was associated with PBC. More recently, a similar lack of association data was reported for the anion exchanger gene \textit{SLC4A2} [72].

Prompted by the xenobiotic PBC theory [21], we also investigated whether genetic variants leading to different xenobiotic metabolism or transport might in turn account for an increased risk of developing the disease. We therefore genotyped several polymorphisms of enzymes involved in the transport and metabolism of xenobiotics in 169 patients with PBC and 225 healthy controls [73]. Data demonstrated that no polymorphism was associated with PBC susceptibility, while a weak association of the cytochrome P450 \textit{CYP2E1} c2 allele with disease severity was observed in a small subgroup of patients.

Recent studies demonstrated that copy number variations are found in patients with PBC, as in the case of an intragenic region on chromosome 4 called MER115. This was identified during investigation regarding microbial agents using representational difference analysis [74]. The observation that keratin mutations are more frequently encountered in PBC cases and reflect the disease phenotype [75] is also of note.

\textbf{Genome-wide studies come of age}

More recently, the first genome-wide case-control association study was reported in PBC cases from Canada and the US [76] and reported significant associations of PBC with \textit{IL-12A}, \textit{IL-12RB2}, and \textit{STAT4} polymorphisms. The study benefited from sufficient statistical power due to the inclusion of 536 patients with PBC and 1,536 controls genotyped for over 300,000 SNPs, and has to be regarded as the current state-of-the-art study into the genetic basis of PBC, although new and more powerful genotyping tools are becoming available. The role of \textit{IL-12} was most recently supported by experimental data from our group demonstrating in a PBC animal model that the \textit{IL-12p40} gene is crucial to autoimmunity development [77], thus proving an ideal link between genomic studies and disease pathogenesis, with potential therapeutic implications.

\textbf{The sex chromosome connection in PBC}

Similar to other autoimmune diseases commonly diagnosed in women after the menopause [78], fetal microchimerism has been suggested in PBC, with the hypothesis of higher prevalence of small amounts of fetal (paternal) DNA found in mothers with PBC [79]. First, it was suggested that the presence of fetal DNA in the liver of affected women years after pregnancy might predispose to PBC [80]; however, independent findings have not confirmed this hypothesis [81,82]. Genes on the X chromosome are critical to the maintenance of physiological sex hormone levels and, more importantly, of immune responsiveness [83]. Invernizzi and colleagues reported age-dependent enhanced monosomy X in the peripheral white blood cells of women with PBC [84], and later data suggested that the X chromosome loss is preferential (that is, it more commonly involves the paternal or maternal chromosome) [85]. This observation seems to indicate a polygenic model for PBC, with an X-linked major locus of susceptibility in which genes.
The candidate genes were often chosen based on a weak component weakness of the available studies in PBC genetics, as management? This constitutes possibly the most prominent insights about disease pathogenesis, treatment or increase our understanding of the disease or lead to new clinical applications of these variants for personalized medicine in PBC [101]. We suggest that only the integration of genomic data with findings from epigenetics and microRNA research [102], possibly through the use of antisense oligomers, will provide a pragmatic use for the gathered evidence.

**Abbreviations**

ABC, ATP binding cassette; AMA, antimitochondrial antibody; ANA, antinuclear antibody; CTLA-4, cytotoxic T lymphocyte antigen-4; CYF, cytochrome P450; HLA, human leukocyte antigen; IgM, immunoglobulin M; IL, interleukin; MHC, major histocompatibility complex; Nup62, nucleoprotein p62; NPC, nuclear pore complex; PBC, primary biliary cirrhosis; SLE, systemic lupus erythematosus; SNP, single nucleotide polymorphism; TNF, tumor necrosis factor; VDR, 1,25-dihydroxyvitamin D receptor.

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**Competing interests**

The authors declare that they have no competing interests.

**Authors’ contributions**

CS performed the literature search and wrote a major part of the manuscript, NT edited the manuscript and made significant additions, AA contributed to the literature search and data discussion, MEG mentored the co-authors and contributed to the manuscript writing.

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