Primary Biliary Cirrhosis: Family, Genes, and Bugs

George F. Mells

Population-based case-control association studies of primary biliary cirrhosis (PBC) have identified several risk factors that are associated with the disease. These include a personal history of autoimmunity, a family history of PBC, cigarette smoking, use of hair dye or nail varnish, and a history of urinary tract infections.¹

There is strong evidence that PBC is a heritable condition. Some 1.33%-6.4% of PBC patients have a family history of the disease (Table 1).¹⁻⁶ The sibling relative risk (λ_s) for PBC is estimated to be 10.5, which is similar to that of other complex disorders (Table 2).⁶ It has been shown in large case-control association studies that having a first-degree relative (FDR) with PBC is a strong risk factor for developing the disease, with an odds ratio ~ 10 .^{1,7} In a study of eight monozygotic and eight dizygotic twin pairs, the pairwise monozygotic concordance rate for PBC was 0.63 compared with a dizygotic concordance rate of zero.⁸ Furthermore, up to 15% of FDRs of PBC probands have antimitochondrial antibodies (AMAs) with normal liver biochemistry (asymptomatic AMAs), and up to 20% of FDRs of PBC probands have an autoimmune condition other than PBC.^{9,10}

These observations suggest that PBC is a complex disorder, meaning that it is caused by a complex interaction of genetic and environmental factors. In recent years, there have been major efforts to delineate the genetic architecture of PBC. To date, four genome-wide association studies and two iCHIP studies of PBC have been reported (Table 3). Altogether, these studies have confirmed the well-established human leukocyte antigen (HLA) association and identified 27 non-HLA risk loci for the disease (Table 4).¹¹⁻¹⁷ Of note, many loci associated with PBC are also associated with other autoimmune conditions (e.g., Sjogren syndrome), suggesting that some autoimmune disorders might have a common genetic basis.

Candidate genes at PBC risk loci function at multiple levels of the immune system. It seems that many candidate genes for PBC contribute to innate immune responses and the biological cascade by which a T_H1 -type adaptive immune response is (or is not) established (Fig. 1). For example, *SPIB*, *IRF5*, and *IRF8* each contribute to the development of dendritic cells.¹⁸⁻²⁰ In antigen-presenting cells (APCs), signaling by pattern recognition receptors is mediated by *NF- κ B* and *IRF5*, and negatively regulated by *RPS6KA4*, while signaling by *TNFRSF1A* is mediated by *NF-*

TABLE 1 Proportion of PBC Patients with a Family History of the Disease

Reference	Patients with a Family History of PBC	Total Patients	%
Bach and Schaffner ²	26	405	6.40
Brind et al. ³	10	736	1.33
Floreani et al. ⁴	6	156	3.80
Tsuji et al. ⁵	8	156	5.10
Jones et al. ⁶	10	157	6.40
Gershwin et al. ¹	57*	1032	6.00
Corpechot et al. ⁷	8*	221	4.00

*FDR only.

TABLE 2 Heritability of Selected Autoimmune or Immunomediated Disorders, Measured by the Relative Sibling Risk

Disease	Relative Sibling Risk
Primary sclerosing cholangitis	9-39
Crohn disease	5-35
Type I diabetes mellitus	15
PBC	10
Psoriasis	4-12
Rheumatoid arthritis	5-10
Ulcerative colitis	6-9

The relative sibling risk (or λ_s) refers to the risk of disease in siblings of disease probands compared with the risk of disease in the general population.

Abbreviations: AMA, antimitochondrial antibody; APC, antigen-presenting cell; FDR, first-degree relative; PBC, primary biliary cirrhosis.

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TABLE 3 Genome-Wide Association Studies and iCHIP Studies of PBC

Reference	Description	Countries	Ethnicity	Discovery Panel			Replication Panel	
				Cases	Controls	SNP Chip	Cases	Controls
Hirschfield et al. ¹¹	North American GWAS	Canada, United States	Caucasian	505	1,507	Illumina Human Hap370 BeadChip	526	1,206
Hirschfield et al. ¹²	Extended replication study of the North American GWAS	Canada, United States	Caucasian		Discovery panel from North American GWAS		857	3,198
Liu et al. ¹³	Italian GWAS	Italy	Caucasian	453	945	Illumina 610K (cases) Illumina 1Mb (controls)		NA
Liu et al. ¹³	GWMA of North American and Italian GWAS discovery panels	Italy, Canada	Caucasian		Discovery panels from North American and Italian GWAS			NA
Mells et al. ¹⁴	WTCCC3 GWAS	United Kingdom	Caucasian	1,840	5,163	Illumina 660W-Quad array (cases) Illumina Human1M-Duo (controls)	620	2,514
Nakamura et al. ¹⁵	Japanese GWAS	Japan	Japanese	487	476	Affymetrix Axiom Genome-Wide ASI 1 Array	787	615
Juran et al. ¹⁶		Canada, Italy, US	Caucasian					
Liu et al. ¹⁷		UK	Caucasian					
Abbreviations: GWAS, genome-wide association study; GWMA, groundwater management area; NA, not available; SNP, single nucleotide polymorphism.

TABLE 4 Risk Loci and Candidate Genes for PBC

Reference	Locus	SNP/RA	OR	P	Candidate Gene(s) in Region
Hirschfield et al. ¹²	1p36	rs3748816/C	1.33	3.15×10^{-8}	<i>MMEL1</i>
Liu et al. ¹⁷	1p31.3	rs72678531/G	1.61	2.47×10^{-38}	<i>IL12RB2</i>
Liu et al. ¹⁷	1q31.3	rs2488393/A	1.28	4.29×10^{-12}	<i>DENND1B</i>
Liu et al. ¹⁷	2q32.2	rs3024921/A	1.62	2.59×10^{-18}	<i>STAT1, STAT4</i>
Liu et al. ¹⁷	3p24.3	rs1372072/A	1.20	2.28×10^{-8}	<i>PLCL2</i>
Liu et al. ¹⁷	3q13.3	rs2293370/G	1.39	6.84×10^{-16}	<i>TMEM39A, POGUT1, TIMMDC1, CD80</i>
Liu et al. ¹⁷	3q25.33	rs2366643/A	1.35	3.92×10^{-22}	<i>IL12A</i>
Liu et al. ¹⁷	4q24	rs7665090/C	1.26	8.48×10^{-14}	<i>MANBA, NFKB1</i>
Liu et al. ¹⁷	5p13	rs6871748/A	1.30	2.26×10^{-13}	<i>IL7R, CAPSL, SPEF2, UGT3A1</i>
Liu et al. ¹⁷	6p21	rs7774434/C	1.57	1.30×10^{-48}	HLA region
Liu et al. ¹⁷	7p14.1	rs6974491/A	1.25	4.44×10^{-8}	<i>ELMO1</i>
Liu et al. ¹⁷	7q32	rs35188261/A	1.52	6.52×10^{-22}	<i>IRF5, TNPO3</i>
Nakamura et al. ¹⁵	9p32	rs4979462/T	1.57	1.85×10^{-14}	<i>TNFSF15</i>
Mells et al. ¹⁴	11q13	rs538147/G	1.23	2.06×10^{-10}	<i>RPS6KA4</i>
Liu et al. ¹⁷	11q23.3	rs80065107/A	1.39	7.20×10^{-16}	<i>CXCR5, DDX6</i>
Nakamura et al. ¹⁵	11q23	rs4938534/A	1.38	3.27×10^{-8}	<i>POU2AF1</i>
Liu et al. ¹⁷	12p13.2	rs1800693/G	1.27	1.18×10^{-14}	<i>TNFRSF1A, LTBR, SCNN1A</i>
Liu et al. ¹⁷	12q24	rs11065979/A	1.20	2.87×10^{-9}	<i>ATXN2, BRAP, SH2B3</i>
Juran et al. ¹⁶	13q14	rs3862738/G	1.33	2.18×10^{-8}	<i>TNFSF11</i>
Liu et al. ¹⁷	14q24	rs911263/T	1.26	9.95×10^{-11}	<i>RAD51B</i>
Mells et al. ¹⁴	14q32	rs8017161/A	1.22	2.61×10^{-13}	<i>TNFAIP2</i>
Liu et al. ¹⁷	16p13.13	rs12708715/G	1.29	2.19×10^{-13}	<i>SOC3, CLEC16A, PRM1, PRM2</i>
Liu et al. ¹⁷	16q24.1	rs11117433/G	1.26	1.41×10^{-9}	<i>IRF8</i>
Liu et al. ¹⁷	17q12	rs17564829/G	1.26	6.05×10^{-14}	<i>ORMDL3, ZPBP2, GSDMB, IKZF3</i>
Liu et al. ¹⁷	17q21.1	rs17564829/G	1.25	2.15×10^{-9}	<i>CRHR1, MAPT</i>
Liu et al. ¹⁷	19p13.2	rs34536443/G	1.91	1.23×10^{-12}	<i>TYK2</i>
Liu et al. ¹³	19q13.3	rs3745516/A	1.46	7.97×10^{-11}	<i>SPIB</i>
Liu et al. ¹⁷	22q13.1	rs2267407/A	1.29	1.29×10^{-13}	<i>SYNGR1, PDGFB, RPL3</i>

Risk loci were identified at a genome-wide level of significance in at least one genome-wide association study or iCHIP study of PBC. For each locus, the results are from the study with strongest evidence of association.

Abbreviations: OR, odds ratio; RA, risk allele; SNP, single nucleotide polymorphism.

κ B and negatively regulated by *DENND1B*.²¹⁻²⁴ In macrophages, *IRF5* promotes differentiation into inflammatory (M1) macrophages that produce *IL-12* and other pro-inflammatory cytokines.²⁵ Naive $CD4^+$ T_H0 cells are activated when the T cell receptor interacts with epitope presented in the peptide-binding groove of class II HLA on APCs, accompanied by the interaction of various costimulatory molecules, including *CD80* and *CD86* on APC with *CD28* on T cells.²⁶ Activated T_H0 cells are driven to differentiate into T_H1 cells by *IL-12* interacting with *IL-12R*. Signals from *IL-12R* are mediated by *TYK2* and *STAT4* and regulated negatively by *SOC3*.^{27,28} It is plausible that variants in these genes might affect this cascade and predispose to immune dysregulation and autoimmunity.

Genetic factors undoubtedly contribute to the etiology of PBC; however, PBC and other complex disorders cannot be explained by genetic factors alone. Environmental factors are also important. In particular, it has been proposed that micro-organisms (such as *Escherichia coli* or *Novosphingobium aromaticivorans*) or xenobiotics (such as synthetic constituents of cosmetics) might be the environmental trigger for PBC.

Molecular mimicry is generally proposed to be the mechanism by which micro-organisms induce disease in susceptible individuals. By this mechanism, prokaryotic antigens homologous to human pyruvate dehydrogenase complex E2

subunit (PDC-E2) stimulate an adaptive immune response that cross-reacts with self-PDC-E2, initiating the disease process.²⁹ Xenobiotics may trigger disease in a similar fashion. Xenobiotics are metabolically activated to electrophilic intermediates that form covalent adducts with proteins. Autoimmunity may occur if the xenobiotic/self-protein adduct is immunogenic. Autoimmunity may persist after exposure to the xenobiotic has ceased if the immune response cross-reacts with the original, unaltered self-protein.³⁰

In support of this hypothesis, it has been shown that AMAs and T cells against human M2 antigens cross-react with antigens from *E. coli* and vice versa.³¹ Similarly, it has been shown that human AMAs cross-react with antigens from *N. aromaticivorans*, while susceptible mice inoculated with *N. aromaticivorans* have been shown to develop a PBC-like disease.³² Furthermore, it has been shown that inoculation of guinea pigs or mice with xenobiotics such as 6-bromohexanoate or 2-octynoic acid leads to a persistent PBC-like illness.³³

Of note, it has also been proposed that PBC might be caused by direct infection of liver cells by a human β -retrovirus closely related to mouse mammary tumor virus. However, this theory is controversial.³⁴

The microbiome might also contribute to development of PBC and other autoimmune conditions. The microbiome refers to all of the micro-organisms that normally

Figure 1 Variants associated with PBC might affect the process by which the T_H1 immune response is established. Immature dendritic cells (DC) are activated by interaction of pathogen-associated molecular patterns (PAMPs) with pattern recognition receptors (PRRs, potentially including *CLEC16A*). Differentiation into inflammatory DCs is promoted by pro-inflammatory cytokines such as tumor necrosis factor, which cause increased expression of *TNF*, *IL-6*, *IL-12*, and *IFN-γ*. Signaling by PRRs is mediated by *NF-κB* and *IRF5*, and negatively regulated by *RPS6KA4*, while signaling by *TNFRSF1A* is mediated by *NF-κB* and negatively regulated by *DENND1B*. Naive $CD4^+$ T_H0 cells are activated by interaction of the T cell receptor (TCR) with complementary antigen, presented in the peptide binding groove of class II HLA on APCs, with costimulation by *CD80* and *CD86* on APC interacting with *CD28* on T cells. Differentiation of the activated T_H0 cell into T_H1 cells is driven by *IL-12*, which interacts with *IL-12R*. Signals from *IL-12R* are mediated by *TYK2* and *STAT4*, which are negatively regulated by *SOCS1*. In turn, T_H1 cells produce *IFN-γ* and *TGF-β*, inducing pro-inflammatory APCs, promoting *IL-12*, and suppressing *IL-4*, thereby sustaining the T_H1 response. Adapted with permission from *Genetics of Primary Biliary Cirrhosis*. Copyright 2013, John Wiley & Sons Ltd.

inhabit environmentally exposed surfaces (such as the skin, mouth, large bowel, and vagina). It has been shown that the microbiome influences development of the immature immune system as well as immune responses of the mature immune system.³⁵ Significant changes in the composition of the microbiome (“dysbiosis”) might therefore

lead to immune dysregulation and predispose to autoimmunity. Indeed, dysbiosis has been linked to type I diabetes mellitus, inflammatory bowel disease, and psoriasis.³⁶

It is plausible that the genome, microbiome, and molecular mimicry are linked. For example, a high-risk genome or

high-risk microbiome may render the individual more susceptible to autoimmunity, and the autoimmune process may finally be triggered by exposure to a bacterial or xenobiotic mimotope of PDC-E2. Exposure to a mimotope may be unnecessary if genetic variants and/or dysbiosis lead to immune dysregulation sufficient to cause spontaneous loss of tolerance to PDC-E2 and other self-antigens. The rela-

tionship between the genome and microbiome is an exciting subject for research in the near future. ■

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