The Genetics and Epigenetics of Primary Biliary Cholangitis

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KEYWORDS

• Autoimmunity • Genome-wide association studies • X chromosome
• X chromosome inactivation • Methylation • microRNA

KEY POINTS

- Although familial studies indicate that genetic predisposition plays a crucial role in the development of primary biliary cholangitis (PBC), epigenetic modifications and environment factors are also involved.
- Genome-wide association studies have not identified non-HLA candidate genes that are specific to the development of PBC and how HLA alleles influence the susceptibility of PBC is unclear.
- Differences in PBC candidate genes between Europe/North America and Japan/China suggest there are unknown genetic risks/protecting factors that are yet to be identified.
- Methylation profiling and altered X chromosome architecture might reveal the reason for the striking female predominance in PBC.
- MicroRNAs are not only important biomarkers for diagnosis or defining treatment responses in PBC, but also demonstrated to be associated with its immunopathology.

INTRODUCTION

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease; it is an autoimmune reaction targeted to intrahepatic biliary epithelial cells (BECs), eventually resulting in cirrhosis and hepatic failure, without appropriate treatment.[1,2] Histopathologically, it is characterized as chronic nonsuppurative destructive cholangitis with granuloma formation in the liver, and degeneration and necrosis of BECs elicit destructive changes and lead to the disappearance of small or middle-sized intrahepatic bile ducts.[3] PBC is considered as a prototypic autoimmune disease for the following reasons. First,

The authors have nothing to disclose.

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Clin Liver Dis 22 (2018) 443–455
https://doi.org/10.1016/j.cld.2018.03.002 liver.theclinics.com

like other autoimmune diseases, PBC mainly affects middle-aged women with a striking female predominance; the male:female ratio is 1:9 (**Table 1**). Second, a high prevalence of other autoimmune diseases, including Sjogren syndrome and chronic thyroiditis, as comorbidities is noted.[4,5] Third, disease-specific autoantibodies, anti-mitochondrial antibodies (AMAs), are detected in the sera of more than 90% of patients with PBC and are scarcely found in patients without PBC.[6,7] Finally, dense infiltrates consisting of T and B lymphocytes are histologically found in the vicinity of affected intrahepatic bile ducts.[8]

Although the etiology of PBC has not yet been completely elucidated, PBC is generally accepted to be a multifactorial disease and is considered to be caused by the interaction of both genetic background and environmental triggers.[9,10] PBC results from the combination of "bad genes and bad luck"; individuals having predisposed genetic factors develop PBC because of environmental triggering effects. Recent innovative technologies, including genome-wide association studies (GWAS), have identified numerous non–human leukocyte antigen (HLA) risk loci contributing to the susceptibility of PBC. However, the results of GWAS are largely disappointing; the relative risk of each gene is rather low, and many of the loci are not associated with protein coding sequences.[11,12] Thus, as in other autoimmune diseases,[13–15] recent studies have been focusing on the epigenetic mechanisms that would link genetic predisposition and environmental triggering factors to elucidate the etiology of PBC. In this review, we summarize recent findings regarding genetic as well as epigenetic mechanisms that would possibly provide promising tools to reveal the molecular etiology of PBC as well as develop new individualized treatment strategies based on the stratification of risk for the progression of the disease.

GENETICS OF PRIMARY BILIARY CHOLANGITIS

Like many other autoimmune diseases,[11,16] PBC has been shown to be associated with genetic predisposing factors that play a crucial role in its development, and possibly progression. Epidemiologic data suggest an increased prevalence of patients

Table 1
Incidence and prevalence of primary biliary cholangitis (published after 2010)

Country	No. of Patients	Incidence[a] (95% CI)	Prevalence[a] (95% CI)	Male (%)	Year
Europe and America					
Iceland[66]	168	2.5	38.3	18	2012
Southern Israel[81]	138	2	25.5	5.1	2012
North East England[82]	982	4.51 (4.11–4.91)	NA	10	2014
Netherlands[83]	992	1.1	13.2	14	2014
North Italy[68]	2970	1.67 (1.44–1.91)	11.1 (10.9–11.3)	33	2016
Denmark[68]	722	1.14 (1.06–1.23)	11.5 (11.3–11.8)	21	2016
USA (Wisconsin)[84]	79	4.9	NA	5	2017
Greece[67]	482	NA	58.2	13.5	2017
Asia and Pacific					
Southern China[85]	4	NA	49.2 (12.8–109.3)	25	2010
New Zealand[86]	71	0.8 (0.1–1.6)	9.9 (7.1–12.7)	8	2012
South Korea[40]	2824	0.86	4.75	16	2016

Abbreviations: CI, confidence interval; NA, not applicable.
[a] Per 100,000 population.