GASTROENTEROLOGY 2013;144:1357–1374

REVIEWS IN BASIC AND CLINICAL GASTROENTEROLOGY AND HEPATOLOGY

Robert F. Schwabe and John W. Wiley, Section Editors

The Genetics of Complex Cholestatic Disorders

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Cholestatic liver diseases are caused by a range of hepatobiliary insults and involve complex interactions among environmental and genetic factors. Little is known about the pathogenic mechanisms of specific cholestatic diseases, which has limited our ability to manage patients with these disorders. However, recent genome-wide studies have provided insight into the pathogenesis of gallstones, primary biliary cirrhosis, and primary sclerosing cholangitis. A lithogenic variant in the gene that encodes the hepatobiliary transporter ABCG8 has been identified as a risk factor for gallstone disease; this variant has been associated with altered cholesterol excretion and metabolism. Other variants of genes encoding transporters that affect the composition of bile have been associated with cholestasis, namely *ABCB11*, which encodes the bile salt export pump, and *ABCB4*, which encodes hepatocanalicular phosphatidylcholine floppase. In contrast, studies have associated primary biliary cirrhosis and primary sclerosing cholangitis with genes encoding major histocompatibility complex proteins and identified loci associated with microbial sensing and immune regulatory pathways outside this region, such as genes encoding *IL12*, *STAT4*, *IRF5*, *IL2* and its receptor (*IL2R*), *CD28*, and *CD80*. These discoveries have raised interest in the development of reagents that target these gene products. We review recent findings from genetic studies of patients with cholestatic liver disease. Future characterization of genetic variants in animal models, stratification of risk alleles by clinical course, and identification of interacting environmental factors will increase our understanding of these complex cholestatic diseases.

Complex cholestatic diseases include a range of disorders affecting small and large bile ducts and the gallbladder.[1] To date, development of rational interventions for individuals with specific cholestatic disorders has been hampered by gaps in understanding disease pathogenesis. However, recent developments in identifying genetic influences (see Appendix for definitions) have begun to address an unmet need for rational treatment. The immune-mediated biliary disorders, primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC), represent the most important small and large bile duct diseases. The incidence and prevalence rates for PSC vary from 0 to 1.3 per 100,000 inhabitants/year and 0 to 16.2 per 100,000 inhabitants, respectively, whereas the incidence and prevalence of PBC range from 0.3 to 5.8 per 100,000 inhabitants/year and 1.9 to 40.2 per 100,000 inhabitants, respectively.[2–4] PBC and PSC have been observed in all heritages, and geographic variations are evident with an increased prevalence in northern latitudes. Clustering of PBC has also been reported geographically, for example, in coastal First Nations of British Columbia, where disease has been recorded to be as high as 1 in 4 within generations of well-characterized multiplex families.[5] In contrast, cholesterol gallstone disease is far more common and we have a much clearer understanding of the pathophysiology. Several factors combine to promote gallstone formation, such as supersaturation of bile with cholesterol or bilirubin, gallbladder hypomotility, and an imbalance of crystallization promoters (eg, mucin) and inhibitor proteins.[6] Nevertheless, the incidence of gallstones differs markedly worldwide, reaching 50% in the American Indian population, 15% to 20% in the European population, approximately 10% in the Asian population, and less so in African populations.[7] These differences are not fully explained by environmental factors such as phys-

Abbreviations used in this paper: AH, ancestral haplotype; AMA, antimitochondrial antibodies; GGT, γ-glutamyltransferase; GWAS, genome-wide association studies; IBD, inflammatory bowel disease; IL, interleukin; LPAC, low phospholipid-associated cholelithiasis; MHC, major histocompatibility complex; PBC, primary biliary cirrhosis; PDC-E2, pyruvate dehydrogenase complex E2; PFIC, progressive familial intrahepatic cholestasis; PSC, primary sclerosing cholangitis; Th, T-helper; TNF, tumor necrosis factor.

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2013.03.053

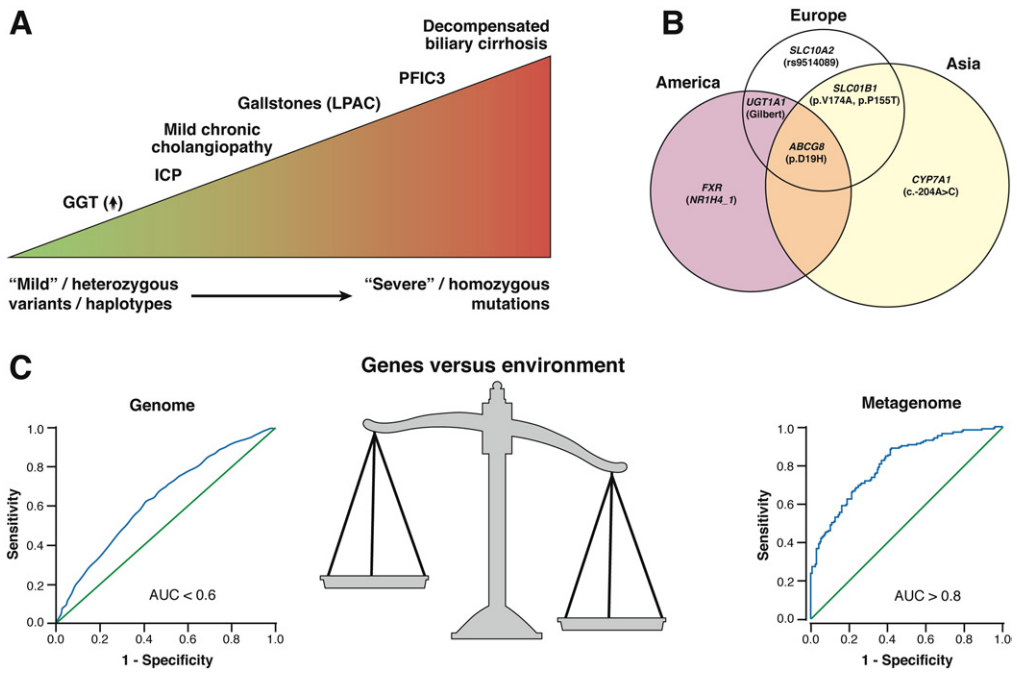

Figure 1. Interaction of genes and environment in complex cholestatic disease. (*A*) Variations in severity of disease manifestation are observed with different genotypic variants in the *ABCB4* encoding the biliary phosphatidylcholine transporter. Heterozygous *ABCB4* variants encompass mild phenotypes, whereas homozygous deficiency leads to more severe diseases (ie, biliary cirrhosis and chronic liver failure). Specific genotypes might also contribute to chronic cholestasis and/or modify disease progression in patients with PBC and PSC. (*B*) Venn diagram illustrating lithogenic variants that have been confirmed in replication studies. The size of each circle reflects the estimated number of adults with gallstones in each continent. Previous studies showed that Latin American populations have the highest (~30%) incidence of gallstone disease, with intermediate frequency of the disease in Europe (15%–20%) and lowest relative frequency in Asia (5%–6%). (*C*) The gut microbiome is more predictive of type 2 diabetes than current candidate loci derived by GWAS. A comparison of data derived from candidate type 2 diabetes loci[108,109] and a selection of genes derived from metagenomic analyses of the gut microbiome from individuals with type 2 diabetes[107] shows a superior correlation with the microbiome (based on the original cited data). ICP, intrahepatic cholestasis of pregnancy.

ical inactivity or high-calorie, high-carbohydrate, and low-fiber diets, or medications.[8,9]

The dynamic genetic interactions that contribute to disease manifest at various levels. Some genes determining disease risk may only do so by imparting variability in how individuals respond to a particular environmental challenge. Others may express the consequence of genetic variation in a graded manner in as much as a single gene can be responsible for a wide phenotype spectrum depending on background genetic variability. A good example is provided by recognizing how *ABCB4* variants can lead to disease ranging from mild elevations of γ-glutamyltransferase (GGT) levels as well as cholestasis of pregnancy and intrahepatic gallstones with premature cholelithiasis to early development of biliary cirrhosis in childhood (Figure 1*A*). The clinical spectrum of disease associated with this single gene aptly shows the mechanistic complexity of cholestatic disease. Genetic variation in structural proteins may also contribute to disease even if not directly related to the primary process mechanistically. For example, the association of keratin variants with PBC[10] suggests how mutations in structural proteins can act as genetic modifiers and may be related to an accelerated liver disease phenotype alongside the overall genetic complexity of disease.

Heritability and the Role of the Major Histocompatibility Complex

Heritability is difficult to quantify and confounded by sharing of environmental triggers within close relatives. It is usually estimated by concordance rates in monozygotic versus dizygotic twins or by dividing the prevalence of disease among siblings with that of the general population (ie, sibling relative risk, λ_s). Collectively, such estimates suggest that the development of PBC and PSC is comparable to the 10-fold to 20-fold increased relative risk observed with other immune-mediated conditions such as inflammatory bowel disease (IBD). More precise estimates have been derived from countries with registries recording outcomes for disease for the population as a whole. For example, studies performed in ~30,000 Swedish twins with symptomatic gallstone disease have estimated the heritability to be approximately 25%.[11]

Before the advent of genome-wide association studies (GWAS), variants within the major histocompatibility complex (MHC) on chromosome 6p21 were the only robust candidates that were clearly associated with PBC and PSC. More than 30 years ago, PSC was linked with HLA-B8, a known phenotypic marker for ancestral haplotype