Genetic Risks Link Autoimmune Hepatitis to Other Autoimmune Liver Disease

See "Genome-wide association study identifies variants associated with autoimmune hepatitis type 1," by de Boer YS, van Gerven NMF, Zwiers A, et al, on page 443.

Autoimmune hepatitis (AIH) is a cryptic, immune-mediated hepatitis accompanied by significant morbidity and mortality, which presents as a spectrum of acute and chronic liver injury.[1] Present medical therapy is limited, frequently lifelong, and commonly accompanied by side effects.[2] To overcome an unmet patient need for better recognition, diagnosis, and management of AIH, fundamental advances into the mechanisms of disease are needed. Classically, AIH is considered to have many origins, and likely represents a compendium of different precipitating insults (eg, drug injury, toxin exposure, viral infection) on a host background of genetic predisposition. Histologic and serologic features of this apparently classical autoimmune illness may also occur in the context of autoimmune bile duct disease[3] (primary biliary cirrhosis [PBC] and primary sclerosing cholangitis [PSC]) and chronic hepatitis C infection,[4] suggesting an overlap in antigenic determinants for the immune-mediated tissue injury in these conditions that are not explained by current models of disease. Mechanistic human and murine studies have been contributory to our current immunophenotypic and immunogenetic concepts of disease. In this month's issue of *Gastroenterology*, investigators now provide further genetic insights, with the publication of the first successful genome-wide association study.[5]

AIH seems to be a syndrome characterized by an imbalance in immunoregulation, in which immune responses (adaptive and innate) to hepatocyte antigens are important, potentially arising on the basis of thymic changes affecting the development of T-cell tolerance.[6,7] Specifically, medullary thymic epithelial cells regulate T-cell tolerance by ectopically expressing self-antigens and eliminating autoreactive T cells. In mice with a conditional deletion of *Traf6* (an E3 ubiquitin protein ligase regulating medullary thymic epithelial cell development), a surprisingly good reproduction of human AIH is evident, supporting the concept that impaired antigen presentation owing to medullary thymic epithelial cell depletion and elimination of autoreactive T cells is relevant to AIH pathogenesis.[8] Concurrent with this, patients harboring mutations in the *AIRE* gene (which controls tissue restricted antigen expression in medullary thymic epithelial cells) suffer with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, a syndrome that includes a high prevalence of AIH.[9]

An enhanced host immunogenetic risk of AIH has been suggested based on reports of familial occurrence and reproducible genetic associations within the *HLA* complex on chromosome 6p21.[10] Up to now, evaluation of the genetics of AIH has focused on small scale, usually non-replicated, candidate gene studies. The utility of large case-control studies with genome-wide surveys of genetic risk has been aptly demonstrated for PBC and PSC.[11,12] It was therefore only a matter of time before AIH was subject to the same genetic scrutiny. The challenge for AIH is the inherent diverse nature of the disease, its variable onset and exact definition, which makes homogenous case ascertainment and accurate phenotyping difficult. Alongside this is the need to adequately power, and replicate, any genome-wide association study given the low risk exerted by genetic variants detected by this study design (odds ratio typically <1.5).[13] On the basis of autoantibody specificity, AIH can be "conveniently" classified into type 1 and type 2 disease. Patients with type 1 disease are defined predominantly by the presence of circulating antinuclear antibodies and/or smooth muscle antibodies; antibodies against soluble liver antigen/liver-pancreas are also found. Those with type 2 disease (commonly European and pediatric in onset) are characterized by the presence antibodies to liver kidney microsomal antigen type-1 and anti-liver cytosol type 1. Furthermore, AIH can be considered as a standalone illness (albeit associated with other systemic autoimmune disorders such as celiac disease, thyroiditis, and rheumatoid arthritis) or a component of autoimmune disease involving the bile ducts (PBC and PSC). de Boer et al[5] present the first multicenter genome-wide association study of risk of developing type 1 AIH. In their genomic study focused on European patients, the authors sensibly restrict their analysis to initially Dutch and then German patients with type 1 AIH, excluding the small number of type 2 patients as well as patients with concurrent PBC and PSC. Using this approach, and a combination of genetic analytical methodologies and statistical tools, a robust, hypothesis-free, evidence base of the genetic architecture of AIH is provided. This for the first time demonstrates a profound importance of the HLA complex alongside potential new non-HLA associations. The findings are contextualized by alignment of the genetic signature of AIH to that already known for PBC and PSC.

Thus, de Boer et al provide some evidence to associate AIH with variants of *SH2B3* (rs3184504, 12q24; $P = 7.7 \times 10^{-8}$) and *CARD10* (rs6000782, 22q13.1; $P = 3.0 \times 10^{-6}$). Although neither of these associations reached the accepted level of significance required to declare "genome-wide significance" ($P < 5 \times 10^{-8}$), the prior association of the *SH2B3* variants with autoimmune diseases suggests that ultimately, with larger cohorts, this observation is likely to be confirmed. For *CARD10*, a more rigorous validation in independent AIH control cohorts is warranted. *SH2B3* is of

interest, given the association between this genomic region and hypothyroidism, type 1 diabetes, celiac disease, rheumatoid arthritis, PBC, and PSC (available from: http://www.genome.gov/gwastudies/). Although caution must always be exercised in relating genomic association studies to biologic function in the absence of appropriate functional confirmation in vitro and in vivo (as well as genetic resolution to map the true "at-risk" variant/gene), this particular gene product is plausibly involved in the pathogenesis of AIH, being associated with all 3 autoimmune liver diseases. SH2B3, also known as the intracellular adaptor LNK, negatively regulates hematopoiesis, cytokine signaling, and inflammation, and influences a variety of signaling pathways mediated by Janus kinases and receptor tyrosine

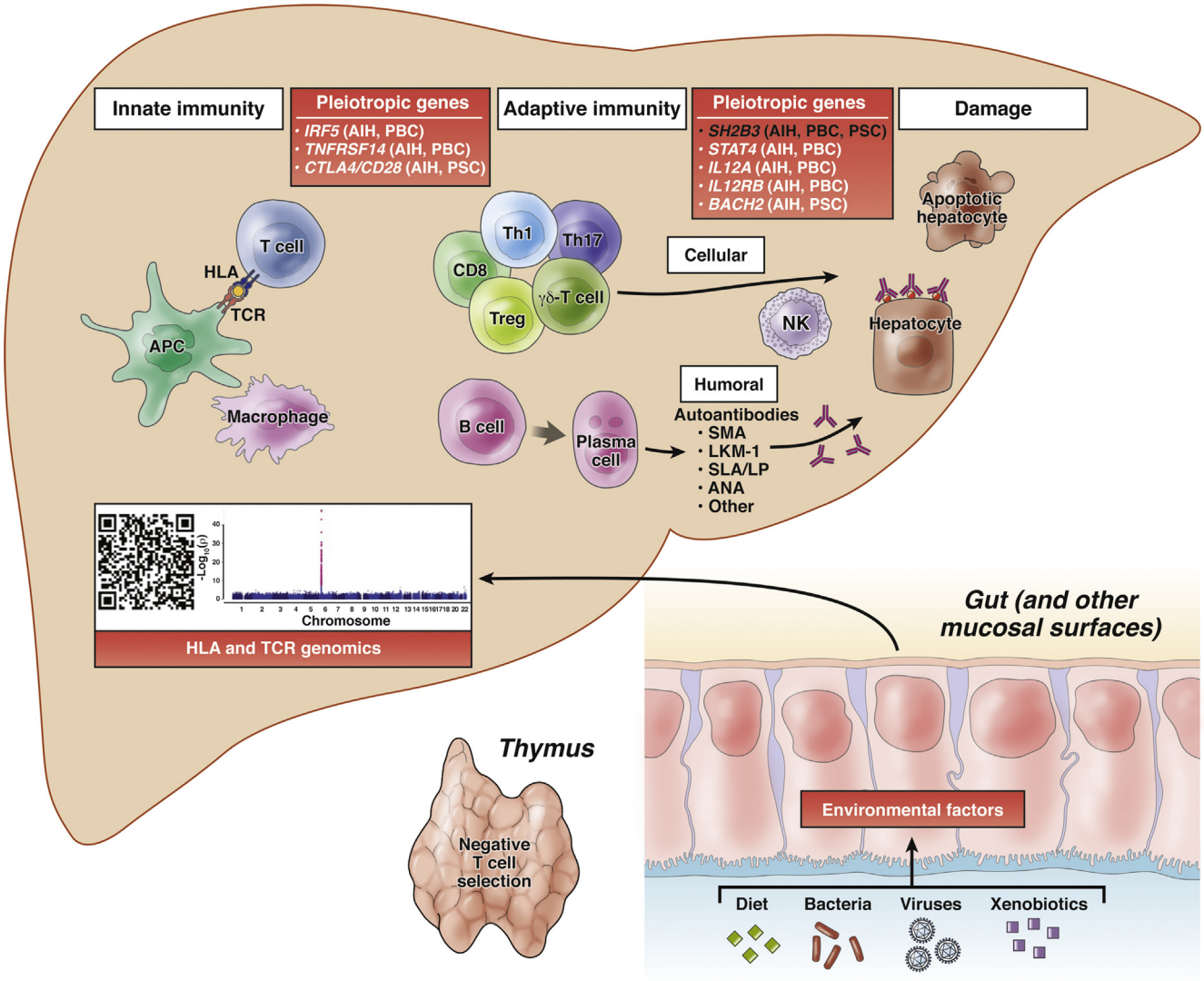

Figure 1. Autoimmune hepatitis (AIH) and its genetics. The overall architecture of the genetics of AIH as determined by the present genome-wide association study resembles that of other autoimmune and autoinflammatory diseases. The general feature of these conditions is that of a predominant HLA association on a background of multiple weaker associations in genes involved in various aspects of immune regulation. Likely, as demonstrated in celiac disease, the HLA association is critical for determining specificity of the humoral (autoantibodies) and cellular immune responses, and may even point to environmental triggers (in the case of celiac disease gluten, but in most cases unknown). The weaker associations in other genetic regions are typically "pleiotropic," that is, they are almost never disease specific according to present disease classification systems, but rather seem to define a general "autoimmune predisposition" (including regulators of central/thymic and peripheral T-cell tolerance) as well as unfavorable features of the immune effector machinery that are involved in tissue damage in autoimmunity. In the "pleiotropic genes" panels, none of these potential risk loci in AIH achieved formal genome-wide significance levels ($P < 5 \times 10^{-8}$), although the *SH2B3* (highlighted in black) association was nominally significant in the replication experiment. Only genes showing associations in other autoimmune liver diseases are shown (ie, excluding *IL13, MPV17L2* and *TNFAIP3* from the presentation). The QR code symbolizes the interaction between the genetically (HLA) determined immune specificity and endogenous and exogenous antigenic triggers. For gene name abbreviations, please see http://www.ncbi.nlm.nih.gov/gene/. APC, antigen-presenting cell; HLA, human leukocyte antigen; NK, natural killer cell; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; TCR, T-cell receptor.