Autoimmune hepatitis is an uncommon disorder characterized by chronic hepatic inflammation that improves after treatment with corticosteroids and other immunosuppressive drugs. The disorder can occur in children and adults of any age but has a particular predilection for girls and young women. The majority of patients present insidiously with malaise, anorexia and arthralgia but a minority have features that are similar or identical to acute hepatitis. Laboratory abnormalities include abnormal liver function tests, elevated serum levels of IgG and the presence in serum of various autoantibodies including antinuclear antibodies, smooth muscle antibodies (antiactin antibodies), soluble liver antigen antibodies and liver-kidney microsomal antibodies. Autoantibody profiles can be used to categorize patients into autoimmune hepatitis types 1 and 2; a categorization that has implications for responsiveness to treatment and prognosis.

The most popular hypothesis for the pathogenesis of autoimmune hepatitis involves an interaction between human leukocyte antigens (HLA), hepatocyte antigens and receptors on T lymphocytes (Fig. 1). HLA antigens are glycopeptides that traverse cell membranes and are involved in the presentation of infectious and other antigens to T lymphocytes. These HLA antigens are highly polymorphic, a characteristic that appears to influence susceptibility to autoimmune disease by effects on discrimination between self and non-self. In autoimmune hepatitis, the candidate self-antigens are the asialoglycoprotein receptor (located on the hepatocyte surface) in type 1 disease and cytochrome P4502D6 or other antigens in the hepatocyte microsomes in type 2 disease. Serotyping for HLA antigens has shown that HLA-DR3 increases the risk of autoimmune hepatitis type 1 by 12–fold in Caucasian populations. An increase in risk has also been associated with HLA-DR4. These findings have been confirmed using HLA genotypes where significant associations have been reported for the HLA haplotype DRB1*0301-DRB3*0101-DQA1*0501-DQB1*0201. The first two alleles of the haplotype correspond to the serologic determinants DR3 and DR52 but whether DRB1*0301 or DRB3*0101 is the primary susceptibility allele has not been resolved. The serotype, HLA-DR3, has also been associated with more severe forms of the disease and with onset at a younger age. In Japan, where HLA-DR3 is rare, HLA-DR4 confers a relative risk for autoimmune hepatitis type 1 of approximately 15.

A variety of viruses including hepatitis A, hepatitis B, hepatitis C, Epstein-Barr virus and measles virus have been implicated as triggers for autoimmune hepatitis. Additional triggers may include drugs such as minocycline, atorvastatin, methyldopa, nitrofurantoin and pemoline. Whether it is relevant that the proposed target antigen for autoimmune hepatitis type 2 is a drug-metabolizing enzyme remains unclear. In relation to the pathogenesis of autoimmune hepatitis, one possibility is molecular mimicry between the offending virus or drug and hepatocyte antigens. In genetically predisposed individuals, this may result in an inappropriate immune response against the hepatocyte, even after elimination of the virus or cessation of the drug.

It is widely believed that the incidence of autoimmune hepatitis has declined, at least in Caucasian populations. This may reflect lower incidence rates for acute viral hepatitis, particularly hepatitis A. The relative importance of other environmental triggers is less clear although case reports have highlighted the potential role of minocycline. The HLA associations described above are not specific for autoimmune hepatitis type 1 as similar associations have been reported for other autoimmune diseases. Furthermore, there is no consensus, as yet, on a role for other polymorphisms that
might influence the function of the T-cell receptor or other components of the immune response.

**Recommended reading**

Manns MP, Vogel A. *Hepatology* 2006; **43**: S132–44.
Primary sclerosing cholangitis (PSC) is a chronic inflammatory disorder of the biliary system that results in progressive fibrosis and strictures of the intrahepatic and extrahepatic bile ducts. Typical radiological changes on retrograde cholangiography are shown in Figure 1. These strictures cause cholestatic liver disease that may progress to end-stage cirrhosis. The disorder has a strong association with inflammatory bowel disease, particularly ulcerative colitis. Although only 5% of patients with ulcerative colitis develop PSC, at least 70% of patients with PSC will either have inflammatory bowel disease or will subsequently develop inflammatory bowel disease. However, despite these associations, the development and outcome of PSC appears to be independent of the activity of colitis and may even occur after proctocolectomy. Although there are equal numbers of men and women with ulcerative colitis, primary sclerosing cholangitis appears to be more common in men (70%). The pathogenesis of PSC continues to be unclear. There is only limited support for hypotheses that attribute biliary inflammation to portal bacteremia, toxic bile acids, biliary infections and ischemic damage. More recently, most of the attention has focussed on disorders of immune regulation that may be common to both PSC and ulcerative colitis. In PSC, markers of altered immunity include elevated serum levels of IgM and the presence in serum of smooth muscle antibodies, antinuclear antibodies and antineutrophil cytoplasmic antibodies (p-ANCA). The latter appear to be directed against a nuclear envelope protein and can be detected in 80–100% of patients with PSC. However, it can also be detected in unaffected family members with PSC as well as patients with ulcerative colitis and other chronic inflammatory disorders. One interesting possibility is that PSC is mediated by long-lived memory T cells that were originally activated in the gut. Recruitment to the liver may be mediated by aberrant expression of chemokines and adhesion molecules on endothelial cells with the subsequent development of biliary inflammation.

There is only limited information on susceptibility genes for PSC. No twin studies have been reported. In family studies, one report indicates that the prevalence of PSC in siblings and first-degree relatives is low at 1.5% and 0.7%, respectively. There are similar risks for inflammatory bowel disease in first-degree relatives of patients with ulcerative colitis. In relation to HLA antigens, patients with PSC have a higher than expected frequency of HLA-B8 and -DR3 and perhaps -DR52a. However, these associations are not specific for PSC since similar associations have been observed in other autoimmune diseases including autoimmune hepatitis. There is also the possibility that accelerated progression of PSC is associated with the heterozygous genotype corresponding to HLA-DR3, -DQ2. Other polymorphisms that have been reported to influence susceptibility to PSC involve the tumor necrosis factor–alpha gene (TNFA), the major histocompatibility class I chain-related gene family (MIC), the stromelysin gene (MMP) and the intercellular adhesion molecule -1 gene (ICAM-1). Two of these genes, TNFA and MIC, map closely to the HLA region on chromosome 6. However, corroborative studies are required before these non-HLA genotypes are accepted as established susceptibility genes for PSC.

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