mechanisms that maintain self-tolerance. As discussed later, some clues about how these mechanisms might be disrupted have come from the analysis of patients with rare inherited autoimmune disorders and from gene knockout mice that develop autoimmune lesions. However, despite the advances in understanding mechanisms of immune tolerance and regulation, it is not known why these may become defective in the majority of common autoimmune diseases.

- **Abnormal display of self antigens.** Abnormalities may include increased expression and persistence of self antigens that are normally cleared, or structural changes in these antigens resulting from enzymatic modifications or from cellular stress or injury. If these changes lead to the display of antigenic epitopes that are not expressed normally, the immune system may not be tolerant to these epitopes, thus allowing anti-self responses to develop.
- **Inflammation or an initial innate immune response.** As discussed earlier, the innate immune response is a strong stimulus for the subsequent activation of lymphocytes and the generation of adaptive immune responses. Microbes or cell injury may elicit local inflammatory reactions resembling innate immune responses, and these may be critical inducers of the autoimmune disease.

Although these are appealing hypotheses, which of these abnormalities actually play a role in a specific autoimmune disease in humans remains largely a matter of speculation.

Role of Susceptibility Genes

Most autoimmune diseases are complex multigenic disorders. It has been known for decades that autoimmunity has a genetic component. The incidence of many autoimmune diseases is greater in twins of affected individuals than in the general population, and greater in monozygotic than in dizygotic twins, proof that genetics contributes to the development of these disorders.

Association of HLA Alleles with Disease. **Among the genes known to be associated with autoimmunity, the greatest contribution is that of HLA genes** (Table 6-7). The most striking of these associations is between ankylosing spondylitis and *HLA-B27*; individuals who inherit this class I HLA allele have a 100-200 fold greater chance (odds ratio, or relative risk) of developing the disease compared with those who do not carry *HLA-B27*. Many autoimmune diseases are associated with different class II *HLA* alleles. Although it is reasonable to postulate that these associations reflect the ability of some HLA molecules to display self peptides, it has been difficult to show that disease-associated HLA molecules do so any better or worse than molecules that are not associated with autoimmunity. Thus, the mechanisms underlying these disease associations remain poorly understood. It is also important to understand that different HLA alleles may contribute to a disease but their presence is not, by itself, the cause of any disease. Thus, in the example of HLA-B27, the vast majority of individuals who inherit this allele never develop ankylosing spondylitis.

Table 6-7 Association of HLA Alleles and Inflammatory Diseases

Disease	HLA allele	Odds Ratio†
Rheumatoid arthritis (anti-CCP Ab positive)‡	DRB1, 1 SE allele¶	4
	DRB1, 2 SE alleles	12
Type 1 diabetes	DRB1*0301-DQA1*0501-DQB1*0201 haplotype	4
	DRB1*0401-DQA1*0301-DQB1*0302 haplotype	8
	DRB1*0301/0401 haplotype heterozygotes	35
Multiple sclerosis	DRB1*1501	3
Systemic lupus erythematosus	DRB1*0301	2
	DRB1*1501	1.3
Ankylosing spondylitis	B*27 (mainly B*2705 and B*2702)	100-200
Celiac disease	DQA1*0501-DQB1*0201 haplotype	7

†The odds ratio reflects approximate values of increased risk of the disease associated with the inheritance of particular HLA alleles. The data are from European-derived populations.
‡Anti-CCP Ab = antibodies directed against cyclic citrullinated peptides. Data are from patients who test positive for these antibodies in the serum.
¶SE refers to shared epitope, so called because the susceptibility alleles map to one region of the DRB1 protein (positions 70-74).
Courtesy Dr. Michelle Fernando, Imperial College London.

In addition to autoimmune diseases, some inherited errors of metabolism, such as 21-hydroxylase deficiency and hereditary hemochromatosis, are also associated with particular HLA alleles (*HLA-BW47* and *HLA-A*, respectively). However, in these cases, the mutated genes causing 21-hydroxylase deficiency and hereditary hemochromatosis happen by chance to be located in the MHC locus, and the linked HLA alleles are innocent bystanders that are not culpable in either of these diseases.

Association of Non-MHC Genes with Autoimmune Diseases. Genome-wide association studies and family studies have shown that multiple non-MHC genes are associated with various autoimmune diseases (Table 6-8). Some of these genes are disease-specific, but many of the associations are seen in multiple disorders, suggesting that the products of these genes affect general mechanisms of immune regulation and self-tolerance. Three recently described genetic associations are especially interesting.

- Polymorphisms in a gene called *PTPN22*, which encodes a protein tyrosine phosphatase, are associated with rheumatoid arthritis, type 1 diabetes, and several other autoimmune diseases. Because these disorders have a fairly high prevalence (especially rheumatoid arthritis), *PTPN22* is said to be the gene that is most frequently implicated in autoimmunity. It is postulated that the disease-associated variants encode a phosphatase that is functionally defective and is thus unable to fully control the activity of tyrosine kinases, which are involved in many responses of lymphocytes and other cells. The net result is excessive lymphocyte activation.
- Polymorphisms in the gene for *NOD2* are associated with Crohn disease, a form of inflammatory bowel disease, especially in certain ethnic populations. NOD2, a member of the NOD-like receptor (NLR) family (discussed earlier), is a cytoplasmic sensor of microbes that is expressed in intestinal epithelial and other cells. According to one hypothesis, the disease-associated