TABLE 373e-1 SIGNIFICANT HLA CLASS I AND CLASS II ASSOCIATIONS WITH DISEASE

	Marker	Gene	Strength of Association
Spondyloarthropathies			
Ankylosing spondylitis	B27	*B*27:02,–04, –05*	++++
Reactive arthritis (Reiter's)	B27		++++
Acute anterior uveitis	B27		+++
Reactive arthritis (*Yersinia, Salmonella, Shigella, Chlamydia*)	B27		+++
Psoriatic spondylitis	B27		+++
Collagen-Vascular Diseases			
Juvenile arthritis, pauciarticular	DR8		++
	DR5		++
Rheumatoid arthritis	DR4	*DRB1*04:01, –04, –05*	+++
Sjögren's syndrome	DR3		++
Systemic lupus erythematosus			
White	DR3		+
Japanese	DR2		++
Autoimmune Gut and Skin			
Gluten-sensitive enteropathy (celiac disease)	DQ2	*DQA1*05:01* *DQB1*02:01*	+++
Chronic active hepatitis	DR3		++
Dermatitis herpetiformis	DR3		+++
Psoriasis vulgaris	Cw6		++
Pemphigus vulgaris	DR4	*DRB1*04:02*	+++
	DQ1	*DQB1*05:03*	
Bullous pemphigoid variant	DQ7	*DQB1*03:01*	+
Autoimmune Endocrine			
Type 1 diabetes mellitus	DQ8	*DQB1*03:02*	+++
	DR4	*DRB1*04:01,–04*	++
	DR3		
	DR2	*DQB1*06:02*	—[a]
Hyperthyroidism (Graves')	B8		+
	DR3		+
Hyperthyroidism (Japanese)	B35		+
Adrenal insufficiency	DR3		++
Autoimmune Neurologic			
Myasthenia gravis	B8		+
Multiple sclerosis	DR2	*DRB1*15:01*	+
	DR2	*DRB5*01:01*	++
Other			
Behçet's disease	B51		++
Congenital adrenal hyperplasia	B47	*21•OH (Cyp21B)*	+++
Narcolepsy	DR2	*DQB1*06:02*	++++
Goodpasture's syndrome (anti-GBM)	DR2		++
Abacavir hypersensitivity	B57	*B*57:01*	++++

[a]Strong negative association, i.e., genetic association with protection from diabetes.

Abbreviation: GBM, glomerular basement membrane.

DRB1 susceptibility allele (usually *DRB1*08* or *-*05*) have a higher relative risk than expected from the additive effect of those genes alone. In juvenile patients with rheumatoid factor–positive polyarticular disease, heterozygotes carrying both *DRB1*04:01* and *-*04:04* have a relative risk >100, reflecting an apparent synergy in individuals inheriting both of these susceptibility genes.

Type 1 Diabetes Mellitus Type 1 (autoimmune) diabetes mellitus (Chap. 417) is associated with MHC genes on more than one haplotype. The presence of both the DR3 and DR4 haplotypes in one individual confers a twentyfold increased risk for type 1 diabetes; the strongest single association is with *DQB1*03:02*, and all haplotypes that carry a *DQB1*03:02* gene are associated with type 1 diabetes, whereas related haplotypes that carry a different DQB1 gene are not. However, the relative risk associated with inheritance of this gene can be modified, depending on other HLA genes present either on the same or a second haplotype. For example, the presence of a DR2-positive haplotype containing a *DQB1*06:02* gene is associated with decreased risk. This gene, *DQB1*06:02*, is considered "protective" for type 1 diabetes. Even some DRB1 genes that can occur on the same haplotype as *DQB1*03:02* may modulate risk, so that individuals with the DR4 haplotype that contains *DRB1*04:03* are less susceptible to type 1 diabetes than individuals with other DR4-DQB1*03:02 haplotypes. There are some characteristic structural features of the diabetes-associated DQ molecule encoded by DQB1*03:02, particularly the capability for binding peptides that have negatively charged amino acids near their C-termini. This may indicate a role for specific antigenic peptides or T cell interactions in the immune response to islet-associated proteins.

Although the presence of a DR3 haplotype in combination with the DR4-DQB1*0302 haplotype is a very high-risk combination for diabetes susceptibility, the specific gene on the DR3 haplotype that is responsible for this synergy is not yet identified.

Rheumatoid Arthritis The HLA genes associated with rheumatoid arthritis (RA) (Chap. 380) encode a distinctive sequence of amino acids from codons 67–74 of the DRβ molecule: RA-associated class II molecules carry the sequence LeuLeuGluGlnArgArgAlaAla or LeuLeuGluGlnLysArgAlaAla in this region, whereas non-RA-associated genes carry one or more differences in this region. These residues form a portion of the molecule that lies in the middle of the α-helical portion of the DRB1-encoded class II molecule, termed the *shared epitope*.

The highest risk for susceptibility to RA comes in individuals who carry both a *DRB1*04:01* and *DRB1*04:04* gene. These DR4-positive RA-associated alleles with the *shared epitope* are most frequent among patients with more severe, erosive disease. Several mechanisms have been proposed that link the shared epitope to immune reactivity in RA. This portion of the class II molecule may allow preferential binding of an arthritogenic peptide, it may favor the expansion of a type of self-reactive T lymphocyte, or it may itself form part of the pMHC ligand recognized by TCR that initiates synovial tissue recognition.

MOLECULAR MECHANISMS FOR HLA-DISEASE ASSOCIATIONS

As noted above, HLA molecules play a key role in the selection and establishment of the antigen-specific T cell repertoire and a major role in the subsequent activation of those T cells during the initiation of an immune response. Precise genetic polymorphisms characteristic of individual alleles dictate the specificity of these interactions and thereby instruct and guide antigen-specific immune events. These same genetically determined pathways are therefore implicated in disease pathogenesis when specific HLA genes are responsible for autoimmune disease susceptibility.