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## Multiple HLA Epitopes Contribute to Type 1 Diabetes Susceptibility.

[Roark CL](#), [Anderson KM](#), [Simon LJ](#), [Schuyler RP](#), [Aubrey MT](#), [Freed BM](#).

### Author information

#### **Abstract**

Disease susceptibility for type 1 diabetes is strongly associated with the inheritance of specific HLA alleles. However, conventional allele frequency analysis can miss HLA associations because many alleles are rare. In addition, disparate alleles that have similar peptide-binding sites, or shared epitopes, can be missed. To identify the HLA shared epitopes associated with diabetes, we analyzed high-resolution genotyping for class I and class II loci. The HLA epitopes most strongly associated with susceptibility for disease were DQB1 A(57), DQA1 V(76), DRB1 H(13), and DRB1 K(71), whereas DPB1 YD(9,57), HLA-B C(67), and HLA-C YY(9,116) were more weakly associated. The HLA epitopes strongly associated with resistance were DQB1 D(57), DQA1 Y(80), DRB1 R(13), and DRB1 A(71). A dominant resistance phenotype was observed for individuals bearing a protective HLA epitope, even in the presence of a susceptibility epitope. In addition, an earlier age of disease onset correlated with significantly greater numbers of susceptibility epitopes and fewer resistance epitopes ( $P < 0.0001$ ). The prevalence of both DQ and DR susceptibility epitopes was higher in patients than in control subjects and was not exclusively a result of linkage disequilibrium, suggesting that multiple HLA epitopes may work together to increase the risk of developing diabetes