

## **Immune response of HLA class II transgenic mice to human Proteolipid protein and identification of encephalitogenic T cell epitopes**

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The advent of human leukocyte antigen (HLA) transgenic (tg) mice has been useful in identification of human class II-restricted T-cell epitopes that may contribute to autoimmune diseases. To investigate the role of individual HLA class II genes in immune responses to human proteolipid protein (PLP), a candidate autoantigen in multiple sclerosis (MS), mice lacking endogenous class II molecules and expressing HLA genes DR2(DRB1\*1502), DR3(DRB1\*0301), DR4(DRB1\*0401 and DRB1\*0402), DQ6(DQA1\*0103/DQB1\*0601), and DQ8(DQA1\*0301/DQB1\*0302), were immunized with overlapping peptides of PLP (human and mouse PLP are 100% homologous). In all tg mice the majority of the dominant T cell epitopes was restricted to aa31-70, 91-110, 141-160, 180-228, 265-277 of the PLP molecules. T-cell response against PLP-91-110 has been found in MS. To investigate the contribution of HLA class II molecules in susceptibility to inflammatory demyelination, transgenic (tg) mice were immunized with PLP-91-110, in Freund's complete adjuvant followed by pertussis toxin. HLA-DR3, HLA- DR3/DQ6, HLA-DR3/DQ8 tg mice developed severe hind limb paralysis with inflammatory lesions and demyelination in the central nervous system. Disease onset was early (12-15 days) in DR3/DQ8 tg mice as compared to DR3 or DR3/DQ6 mice (20-24 days). However most severe disease pathology in both spinal cord and brain was seen in DR3/DQ6 and DR3/DQ8 tg mice as compared to DR3 tg mice, which had inflammation only in spinal cord. HLA-DQ6, -DQ8, -DR2 and HLA-DR4 tg mice did not develop clinical symptoms of EAE. This humanized mouse model for MS will be valuable in deciphering the role of HLA molecule and autoantigen in MS.