

PHENOTYPIC DISSECTION AND GENETIC EPISTASIS REVEAL THREE SEPARATE SUSCEPTIBILITY LOCI IN CIA5/EAE3

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Identification of genes controlling complex diseases like arthritis has proven to be difficult and work in animal models will pave the way to tell us how low penetrant genes interact to allow disease. We have dissected a QTL earlier identified to control both models for multiple sclerosis (experimental autoimmune encephalomyelitis, EAE) and rheumatoid arthritis (collagen induced arthritis, CIA). Congenic strains showed a low penetrance for both diseases. The QTL interacts with another locus on chromosome 15 and an advanced intercross breeding of the two congenic strains for 8 generations, a partial advanced intercross, accumulated enough power to identify 3 separate loci (Cia5, Cia21 and Cia22) within the original QTL on chromosome 3. Each of these loci was found to control different phases of arthritis and to operate preferentially in an epistatic interaction with loci on chromosome 15. The penetrance of these new loci has been improved through the more precise phenotypic and genetic analysis allowing a further positional cloning procedure to identify the underlying genes.