IDENTIFICATION OF ARTHRITIS PROMOTING NON-OBESE DIABETIC GENES IN THE CIA9 LOCUS USING DIFFERENT GENETIC STRATEGIES

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Background In the gene segregation experiment between susceptible B10.Q and protective NOD.Q mice strains, two strong loci associated with collagen-induced arthritis (CIA) were found, disease-promoting locus on chromosome 1 named CIA9 and a disease-protective locus on chromosome 2, named CIA2. NOD allele on CIA9 locus promotes arthritis whereas on CIA2 locus it inhibits arthritis development.

Materials and methods The authors used both the classic congenic approach and heterogeneous stock mice to identify arthritis promoting genes in the CIA9 locus. The authors dissected the original CIA9 locus into three minimal fragments namely, CIA9b (165–172.6 Mbp), CIA9c (173–175 Mbp) and CIA9i (170.9–173.4 Mbp) by generating three congenic lines.

Results Fragments CIA9b and CIA9c had no effect on CIA and collagen-antibody induced arthritis (CAIA). On the other hand, CIA9i fragment containing a cluster of FcγR genes promoted CIA and, CAIA induced by a monoclonal antibody cocktail containing four antibodies of γ2a and γ2b isotypes. Interestingly, IgG subclass dependency of CIA9i gene segment in arthritis development was ascertained using CII-specific γ2a or γ2b subclass antibodies. Furthermore, the significance of FcγR locus controlling CIA could be confirmed by analysis of the Northport heterogeneous stock cohort, a cross between eight inbred strains involving higher recombinant resolution.

Conclusions The data from congenic approach and HS cross thus suggest increased susceptibility to arthritis of CIA9 locus is due to polymorphisms in the FcγR region.