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Whole genome scan of a murine model of RA

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Keywords

Genetics, murine model, proteoglycan, RA, whole genome scan

Context

RA is a complex disease with both environmental and genetic factors implicated in the disease etiology. Animal models are useful for studying the genetics of autoimmune diseases, such as systemic lupus erythematosus (SLE) and insulin-dependent diabetes mellitus (IDDM), although a spontaneous animal model for RA is not available, at least not in rodents. Polyarthritis can be induced in animals by cartilage components such as type II collagen and proteoglycan. PGIA occurs only in genetically susceptible animals, such as BALB/c mice. When immunized with human PG, BALB/c mice develop progressive polyarthritis and later develop spondylitis. To identify the loci linked to PGIA susceptibility using whole genome screening of (BALB/c x DBA/2) F_2 hybrids.

Significant findings

While inbred BALB/c mice were 100% susceptible to PGIA upon immunization with PG, other strains sharing the same H2d haplotype were resistant. In addition, congenic BALB/c mice with H2k or H2b were partially or completely resistant, suggesting that MHC genes play a role in development of arthritis.

Arthritic mice developed autoantibodies more frequently than nonarthritic mice (75% versus 54%, respectively), though higher titers of the antibodies were observed in nonarthritic mice, suggesting that autoantibodies on their own are not enough to confer disease susceptibility. Only 15% of the F_2 hybrids developed arthritis.

WGS analysis was based on SSLP with average spacing of 15 cM. Twelve QTLs were found to be linked to PGIA, designated Pgia1 through Pgia12. Six were linked to autoantibody production, four were associated with the inflammation trait and two were linked to both phenotypes. Most of the QTLs originated from the BALB/c background, and only two loci were of DBA/2 origin.

Comments

This study confirms previous reports on the genetics of complex diseases and demonstrates that different phenotypes are controlled by different genetic loci. However, loci linked to proteoglycan-induced arthritis (PGIA) seem to differ from those linked to arthritis induced by other antigens. A meta-analysis of genetic loci differences found in animal models would be a useful way of applying results to determining the causes of rheumatoid arthritis (RA).

Methods

Animals were immunized with human cartilage PG aggrecan emulsified with adjuvant (complete and incomplete Freund's) and injected intraperitoneally. Cumulative arthritis scores were generated and antibody and T-cell responses to PG were measured. Whole genome screening (WGS) was carried out using 106 simple sequence length polymorphism (SSLP) markers in 423 F_2hybrids. Genetic maps were constructed using MapMarker/EXP software, and the linkage of potential quantitative trait loci (QTLs) were analyzed using MapMarker/QTL software.

References

1. Otto JM, Cs-Szabo G, Gallagher J, Velins S, Mikecz K, Buzas EI, Enders JT, Li Y, Olsen BR, Glant TT: Identification of multiple loci linked to inflammation and autoantibody production by a genome scan of a murine model of rheumatoid arthritis. Arthritis Rheum. 2000, 42: 2524-2531.