Identification of Genes Controlling Collagen-Induced Arthritis in Mice: Striking Homology with Susceptibility Loci Previously Identified in the Rat

Hai-Tao Yang, Johan Jirholt, Lars Svensson, Mats Sundvall, Liselotte Jansson, Ulf Pettersson and Rikard Holmdahl

*J Immunol* 1999; 163:2916-2921; http://www.jimmunol.org/content/163/5/2916

References

This article cites 42 articles, 15 of which you can access for free at: http://www.jimmunol.org/content/163/5/2916.full#ref-list-1

Subscription

Information about subscribing to *The Journal of Immunology* is online at: http://jimmunol.org/subscription

Permissions

Submit copyright permission requests at: http://www.aai.org/About/Publications/JI/copyright.html

Email Alerts

Receive free email-alerts when new articles cite this article. Sign up at: http://jimmunol.org/alerts
Identification of Genes Controlling Collagen-Induced Arthritis in Mice: Striking Homology with Susceptibility Loci Previously Identified in the Rat

Hai-Tao Yang,* Johan Jirholt,† Lars Svenssson,† Mats Sundvall,† Liselotte Jansson,† Ulf Pettersson,* and Rikard Holmdahl†‡

The susceptibility to collagen-induced arthritis in the highly susceptible DBA/1 mouse has earlier been shown to be partly controlled by the MHC class II gene Aq. To identify susceptibility loci outside of MHC, we have made crosses between DBA/1 and the less susceptible B10.Q strain, both expressing the MHC class II gene Aq. Analysis of 224 F2 intercross mice with 170 microsatellite markers in a genome-wide scan suggested 4 quantitative trait loci controlling arthritis susceptibility located on chromosomes 6, 7, 8, and 10. The locus on chromosome 6 (Cia6), which was associated with arthritis onset, yielded a logarithm of odds score of 4.7 in the F2 intercross experiment and was reproduced in serial backcross experiments. Surprisingly, the DBA/1 allele had a recessive effect leading to a delay in arthritis onset. The suggestive loci on chromosomes 7 and 10 were associated with arthritis severity rather than onset, and another suggestive locus on chromosome 8 was most closely associated with arthritis incidence. The loci on chromosomes 7, 8, and 10 all appeared to contain disease-promoting alleles derived from the DBA/1 strain.

Interestingly, most of the identified loci were situated in chromosomal regions that are homologous to regions in the rat genome containing susceptibility genes for arthritis; the mouse Cia6 locus is homologous with the rat Cia3, Pia5, Pia2, and Aia3; the locus on chromosome 7 (Cia7) is homologous with the rat Cia2; and the locus on chromosome 10 (Cia8) is homologous with the rat Cia4. The Journal of Immunology, 1999, 163: 2916–2921.

Rheumatoid arthritis (RA) is a chronic, inflammatory disease affecting 1% of the population; it is a self-perpetuating inflammatory process eventually leading to erosion of cartilage and bone in peripheral joints. Genetic, hormonal, and environmental factors contribute to its development (1–3). Studies of monozygotic twins indicate a relatively weak but significant genetic influence with a concordance rate of ~15% (4), and previous investigations clearly indicate a role of the MHC, and in particular the MHC class II DR4 haplotype (5, 6). DR4 is, however, a common haplotype in the general population, and most DR4 carriers do not develop RA, implying that genes outside the MHC region as well as environmental factors contribute to the pathogenesis of RA. Attempts to identify RA-associated genes outside the MHC have been hampered by several factors like poorly defined phenotypic criteria for disease, genetic heterogeneity, and variable penetrance. Thus, despite large efforts, it has been difficult to identify significant loci outside MHC in humans, although some promising results have recently been reported (2, 7, 8). However, animal models have been shown to facilitate the genetic analysis because they allow a better control of genetic heterogeneity and of environmental influences. Recently, a number of different genetic regions controlling both acute and chronic arthritis have been identified in various rat models for RA such as collagen-induced arthritis (CIA) (9), mycobacteria adjuvant-induced arthritis (10), ovalbumin-induced arthritis (11), and pristane-induced arthritis (12). Interestingly, several of the susceptibility loci are shared between the models, which could be explained by the fact that the DA strain was used in all studies. Isolation of susceptibility loci in the mouse should be of particular importance not only for the validation of the importance of the regions in the pathogenesis of arthritis but also for the identification of the responsible genes.

CIA in the mouse is the most widely used model for studies of RA pathogenesis and for screening of new drugs for treatment of rheumatoid disease (13, 14). The disease is induced by immunization with cartilage-specific type II collagen (CII) in CFA. The most sensitive and most commonly used strain is DBA/1. Arthritis in the DBA/1 mouse develops with high a penetrance (80–100%) but is also influenced by environmental factors, such as hormones, light, and stress. In fact, under certain environmental circumstances such as intermale induced stress, arthritis may develop spontaneously (15). The same factors enhance the development of CIA (16). The arthritis susceptibility is genetically controlled, and the MHC class II Ag gene has been shown to contribute (17). The product of the Ag gene presents CII-derived peptides and thereby gives the immune-specific requirements for disease development (18). Interestingly, the Ag molecule structurally and functionally related to the RA-associated DR4 (DRB1*0401/DRA) class II molecule and transgenic mice expressing DR4 are susceptible to CIA (19–21). However, just as in RA there is a significant influence by genes outside MHC, demonstrated by the fact that several Ag-expressing strains are more or less resistant to CIA (14, 22–25). One such strain is the B10.Q, which develops low frequency of

*Beijer Laboratory, Department of Genetics and Pathology, Unit of Medical Genetics, Biomedical Center, Uppsala University, Uppsala, Sweden; † Section for Medical Inflammation Research, Sövegatan 19, Lund University, Lund, Sweden

Received for publication January 11, 1999. Accepted for publication June 14, 1999.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

1 This work was supported by grants from the Swedish Medical Research Council, the Beijer Foundation, The Swedish Rheumatism Association, the King Gustaf V’s 80-Year Foundation, and the Kock and Österlunds Foundations.

2 Address correspondence and reprint requests to Dr. Rikard Holmdahl, Section for Medical Inflammation Research, CMB, Lund University, Box 94, S-22362 Lund, Sweden. E-mail address: rikard.holmdahl@inflam.lu.se

3 Abbreviations used in the paper: RA, rheumatoid arthritis; CIA, collagen-induced arthritis; CII, type II collagen; QTL, quantitative trait locus; LOD, logarithm of odds.

Copyright © 1999 by The American Association of Immunologists

0022-1767/99/0502.00
arthritis induced by the same immunization protocol as used for the DBA/1 mouse. To define quantitative trait loci (QTL) which contribute to collagen-induced arthritis, we have analyzed crosses between B10.Q and DBA/1. Gene segregation experiments using F₂ intercrosses and backcrosses revealed several QTLs originating from both B10.Q and DBA/1.

Materials and Methods

Induction and evaluation of CIA

The DBA/1 mice originated from The Jackson Laboratory, and the B10.Q mice originated from Jan Klein, Tübingen, Germany. They were bred and used in conventional animal facilities under stable infectious, light, temperature, feeding, handling, and caging conditions. Rat CII was prepared as described earlier (26). CIA was induced by intradermal immunization in the base of the tail with 50–100 μg CII emulsified in CFA (Difco, Detroit, MI) as described earlier (16). The mice were 8–10 wk old at the time of immunization, and clinical scoring of arthritis commenced 14 days after immunization.

The clinical severity of arthritis was scored according to a graded scale: 1 point = swelling and erythema in a single joint; 2 points = swelling and erythema in more than 1 joint; and 3 points = severe arthritis of the entire paw. Each mouse could thus obtain a maximal score of 12. The severity trait is the maximal score observed in each individual mouse. The onset trait is the logarithmic value of the onset score excluding unaffected animals. For the calculation of logarithm of odds (LOD) scores, we transformed the onset day values into “onset score” by a two-step calculation to adjust for interexperimental variation, because the F₂ intercross experiments were performed as three different experiments although with identical setup. First, the earliest day of observed onset in each experiment was given a score of 35 and the latest day of observed onset was given a score of 0. An adjustment factor for each experiment was calculated by: 35/day after last observed onset day in the experiment − earliest observed onset day in the same experiment). Secondly, the onset score for every observed onset day in each experiment was calculated by: adjustment factor × (day after last observed onset day − the observed onset day).

In comparison with using only onset score values, the log onset values exclude the influence by the incidence trait and are closer to normal distribution and partly remove epistatic influence (27).

Genotyping

Tail tips were used for preparation of genomic DNA according to a standard protocol (28). PCR was performed in 200 μM dNTP, 1.5 mM MgCl₂, 20 mM Tris-HCl with pH 8.3, 0.5 μM concentrations of forward and reverse primer (Research Genetics, Huntsville, AL), 0.5 U Taq DNA polymerase (Perkin-Elmer, Norwalk, CT), and 20 ng genomic DNA in a final volume of 10 μl. The forward primer was phosphorylated with 0.4 μCi [γ-32P]ATP (3000 Ci/mmol, DuPont, Wilmington, DE) as described before. Amplification conditions were as follows: 94°C for 3 min, followed by 25 cycles of 94°C for 15 s, 55°C for 1 min, 72°C for 1 min 30 s, and a final extension at 72°C for 7 min. The PCR was done in a BioOven (Bio Therm, San Francisco, CA) and/or a MJR PTC-225 thermal cycler (Watertown, MA). The PCR products were size fractionated on 6% polyacrylamide gels (AT-Biochem, Malvern, PA). The gels were either exposed for 12–18 h on Hyperfilm (Amersham, Evanston, IL) or analyzed in a PhosphorImager (Molecular Dynamics, Sunnyvale, CA). All markers were scored either on the film or by a PhosphorImager computer screen by two independent readers.

<table>
<thead>
<tr>
<th>Strain/Cross</th>
<th>% Arthritis</th>
<th>Mean Maximal Severity ± SD</th>
<th>Mean Day of Onset ± SD</th>
<th>% Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DBA/1</td>
<td>75–85</td>
<td>4–7</td>
<td>35–40</td>
<td>90–100</td>
</tr>
<tr>
<td>(B10.Q × DBA/1)F₂</td>
<td>80–100</td>
<td>5–7</td>
<td>35–40</td>
<td>80–100</td>
</tr>
<tr>
<td>F₂ backcross (n = 224)</td>
<td>56</td>
<td>5.6 ± 2.7</td>
<td>39.0 ± 10.4</td>
<td>79</td>
</tr>
<tr>
<td>N3 backcross (n = 132)</td>
<td>52</td>
<td>4.4 ± 2.2</td>
<td>42.1 ± 8.7</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>5.9 ± 2.8</td>
<td>40.4 ± 13.9</td>
<td>69</td>
</tr>
</tbody>
</table>

* For the parental and F₂ mice, data are given as mean values obtained from earlier performed experiments under conditions similar to those of the experiments on F₂ animals.

Linkage analysis

All linkage analyses have been made with the MAPMAKER computer package (29). Order of loci was obtained from the Massachusetts Institute of Technology (Cambridge, MA) database (30) and the Mouse Genome Informatics database. Association of individual markers with phenotypes was established by the use of χ² statistics, assigning animals to the affected and unaffected groups and comparing the genotypes of affected and unaffected animals. Log likelihood of linkage was calculated with MAPMAKER/QTL by using the semiquantitative disease severity trait as well as the semiquantitative disease onset trait (29, 31, 32). As significance and suggestive linkage threshold values, we have followed the guidelines suggested by Lander and Kruglyak (33).

Results

Arthritis penetrance and variance

The highly susceptible parental strain DBA/1 develops 90–100% arthritis in males and 60–100% arthritis in females, whereas the less susceptible strain B10.Q develops arthritis in 20–50% of males and 0–30% of females (Table I). The high variability between different experiments is the result of environmental factors some of which are known such as hormone cycling, light, and stress (15, 24, 34, 35). These factors also influence the observed sex difference; male mice are more susceptible than females. The (B10.Q × DBA/1)F₂ mice are highly susceptible, indicating the presence of dominant genes.

To identify non-MHC QTLs contributing to the disease, 224 (B10.Q × DBA/1)F₂ intercross mice were analyzed for arthritis development (Table I). Of these, 125 (56%) mice developed arthritis, 79% of the male mice and 46% of the females. The score distribution is shown in Fig. 1.

Genome scan of the F₂ intercross mice

After screening of parental DNA with 700 mouse microsatellites, we selected 170 informative markers covering the genome. In total, 55% of the markers were informative, indicating a significant evolutionary distance between the strains. The selected...
170 informative markers gave an 84% coverage based on 10-cM distances and more than 95% coverage based on 20-cM distances. The maximum intermarker distance was 29.9 cM. Our mapping strategy was a 2-step approach: 1) the 92 most severely affected animals were genotyped; and 2) the remaining mice were typed for markers from all regions, showing suggestive linkage. The accuracy of our loci order and interval maps was verified by comparing the genetic map calculated from our data with the published Massachusetts Institute of Technology map and Mouse Genome Informatics map. A few differences between our map and the published maps were found. These differences were corrected before performing Mapmaker/QTL based calculations.

Four QTLs were found in the initial screen, located on chromosomes 6, 7, 8, and 10 (Tables II, Fig. 2). The locus found on chromosome 6 (linked to the markers D6Mit19) gave the highest LOD score of 4.7 with the arthritis onset trait, which explained 16% of the genetic variance. Two peaks could be identified in the LOD score curve (Fig. 2), which may indicate the presence of more than one susceptibility gene although they could not be fully separated. Interestingly, these two peaks on chromosome 6 were related to the gender of the mice (Fig. 3). The incidence trait, analyzed with the nonparametric χ² test, gave a suggestive χ² value of 10.42 with 2 df (p = 0.0055), and the severity trait was not or only very weakly associated (LOD score, 1.5). Taken together, these data suggest that this genetic region contains QTLs that control the disease onset rather than severity. Surprisingly, the disease-promoting allele was dominantly inherited from the B10.Q strain, because a delayed onset of disease was associated with the DBA/1 allele in a recessive manner.

The arthritis susceptibility of the DBA/1 strain was associated with several suggestive loci found on chromosomes 7, 8, and 10. A dominant locus on chromosome 7 was associated with severity (LOD score of 2.8) and incidence (p = 0.0065), and another dominant locus on chromosome 8 (D8Mit205/180) was most strongly associated with the incidence trait (p = 0.006). Lastly, a suggestive locus on chromosome 10 was associated with both severity (LOD score 3.3) and incidence (p = 0.002) following a recessive inheritance pattern.

**Analysis of F₂ backcross mice**

To confirm linkage, we backcrossed F₁ mice to the resistant strain B10Q. Of 86 analyzed (F₁ × B10.Q)F₂ backcross mice, 45 (52%) developed arthritis (Table I). The linkage on chromosome 6 was reproduced in the backcross with the same inheritance pattern and within the same chromosomal region. However, in the backcross

**Table II. Genotype distribution of affected and unaffected mice in the F₂ backcross and N3 backcross experiments**

<table>
<thead>
<tr>
<th>Crosses</th>
<th>Marker</th>
<th>Pos (cM)</th>
<th>Affected</th>
<th></th>
<th>Unaffected</th>
<th></th>
<th>X₁f</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>F₂ backcross</td>
<td></td>
<td></td>
<td>A</td>
<td>H</td>
<td>A</td>
<td>H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D6Mit33</td>
<td>12.9</td>
<td>28</td>
<td>15</td>
<td></td>
<td>20</td>
<td>21</td>
<td>1.67</td>
<td>0.0087</td>
</tr>
<tr>
<td>D6Mit124</td>
<td>20.2</td>
<td>30</td>
<td>15</td>
<td></td>
<td>13</td>
<td>24</td>
<td>6.88</td>
<td>0.0009</td>
</tr>
<tr>
<td>D6Mit186</td>
<td>21.3</td>
<td>28</td>
<td>15</td>
<td></td>
<td>15</td>
<td>26</td>
<td>5.74</td>
<td>0.017</td>
</tr>
<tr>
<td>D6Mit16</td>
<td>21.3</td>
<td>29</td>
<td>14</td>
<td></td>
<td>15</td>
<td>26</td>
<td>6.82</td>
<td>0.0090</td>
</tr>
<tr>
<td>D6Mit188</td>
<td>22.4</td>
<td>30</td>
<td>15</td>
<td></td>
<td>13</td>
<td>26</td>
<td>8.01</td>
<td>0.0047</td>
</tr>
<tr>
<td>D6Mit19</td>
<td>23.5</td>
<td>27</td>
<td>16</td>
<td></td>
<td>18</td>
<td>22</td>
<td>1.97</td>
<td></td>
</tr>
<tr>
<td>D6Mit55</td>
<td>42.6</td>
<td>22</td>
<td>21</td>
<td></td>
<td>22</td>
<td>18</td>
<td>0.17</td>
<td></td>
</tr>
<tr>
<td>N3 backcross</td>
<td></td>
<td></td>
<td>A</td>
<td>H</td>
<td>A</td>
<td>H</td>
<td></td>
<td></td>
</tr>
<tr>
<td>D6Mit124</td>
<td>20.2</td>
<td>34</td>
<td>12</td>
<td></td>
<td>26</td>
<td>30</td>
<td>7.86</td>
<td>0.0092</td>
</tr>
<tr>
<td>D6Mit16</td>
<td>21.3</td>
<td>42</td>
<td>11</td>
<td></td>
<td>39</td>
<td>27</td>
<td>5.49</td>
<td>0.0390</td>
</tr>
<tr>
<td>D6Mit188</td>
<td>22.4</td>
<td>37</td>
<td>13</td>
<td></td>
<td>38</td>
<td>22</td>
<td>1.43</td>
<td></td>
</tr>
<tr>
<td>D6Mit19</td>
<td>23.5</td>
<td>41</td>
<td>15</td>
<td></td>
<td>46</td>
<td>23</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>D6Mit65</td>
<td>40.4</td>
<td>24</td>
<td>14</td>
<td></td>
<td>23</td>
<td>12</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>D6Mit55</td>
<td>42.6</td>
<td>16</td>
<td>14</td>
<td></td>
<td>21</td>
<td>13</td>
<td>1.76</td>
<td></td>
</tr>
</tbody>
</table>

* Distance in centimorgans calculated using the Kosambi function and based on the MIT database. A = homozygous B10.Q; H = heterozygous. χ² calculations have been treated with Yates correction.
experiment, the most significant association was with the D6 MIT188 marker rather than the closely located D6 MIT19 marker that revealed highest LOD score in the intercross experiment, again indicating the possible presence of several loci in this region. The highest LOD score in the backcross experiment was $Z = 2.7$ ($Z$ was calculated by a nonparametric approach) for the onset trait, and the $\chi^2$ test value was 8.01 ($p = 0.0047$, Table II). However, other loci identified in the intercross could not be significantly reproduced, although a trend was noted with the same markers and with the same inheritance pattern as in the intercross experiment. This was not an unexpected outcome, because these loci should increase susceptibility rather than suppress it, a direction that seem to be more sensitive to genetic interactions.

Isolation of the chromosome 6 locus in the N3 generation

To further isolate the chromosome 6 locus on the B10.Q background, $F_2$ backcross mice that were heterozygous for relevant markers on chromosome 6 were mated with B10.Q mice. Of the resulting 132 offspring in the N3 generation of backcrossed mice, 59 (45%) developed arthritis. The N3 backcross mice were genotyped with the same markers on chromosome 6 as earlier used, and the locus could be reproduced ($Z = 2.5$ with marker D6 mit124) for the onset trait and with a significant $\chi^2$ test value ($p = 0.0092$) (Table II).

Comparison with homologous regions in the rat

Because several highly significant loci associated with CIA in the rat has been identified, we compared the homologous regions in the rat with our mouse loci. Strikingly, most of the major non-MHC rat loci could be reproduced in our cross (Fig. 4); Cia2 on rat chromosome 1 is homologous with Cia7 on mouse chromosome 7, Cia3 on rat chromosome 4 is homologous with Cia6 on mouse chromosome 6, and Cia8 on rat chromosome 7 is homologous with Cia8 on mouse chromosome 10.

Discussion

In a cross between the DBA/1 strain, which is highly susceptible for CIA, and the relatively resistant B10.Q strain, we have identified four regions that show suggestive or significant linkage with arthritis susceptibility. At one of these loci, present on chromosome 6, the DBA/1 allele was surprisingly associated with a delayed onset of disease and transfer of this region to the B10.Q background delayed arthritis onset. The locus appeared to control the onset of arthritis rather than the severity. Because the linkage was significant in the intercross experiment on the genome wide level and reproduced in the backcrosses, we designate this locus Cia6. The Cia1 locus is the MHC class II gene Aq (17) and another locus was recently found on chromosome 3 in a cross between the
RIII/SJ and the B10.RII strains that was designated Mcia2, now redesignated to Cia5 (36). Most recently, a locus with suggestive linkage close to but not similar with Cia6 as well as two loci on chromosome 2, one of which most likely correspond to a deletion of the complement C5 gene (25), was identified in a cross between the resistant SWR and the DBA/1 strain and suggested to be numbered Cia2–4 (37).

Surprisingly, we were unable to identify significant loci in the B10.Q × DBA/1 cross that could explain the higher susceptibility to CIA of the DBA/1 mouse. Suggestive linkages were found on chromosomes 7, 8, and 10, and these could at least partly explain the higher susceptibility of the DBA/1 mouse. The effects of these loci were seen on the incidence and severity of arthritis rather than on disease onset. Most likely, additional minor loci are present but were impossible to detect in our experiment. Part of the difficulties in reaching significance and thus in detecting additional loci may be the result of the high influence by environmental factors on the strains used in our cross, and possibly also stochastic events, leading to low penetrance and high variability of disease expression. For example, the DBA/1 mice spontaneously develop arthritis if they are stressed, an influence that may also enhance the development of CIA (16). In addition, the DBA/1 mouse is prone to effects by many other variable factors such as sex hormones and light (35, 38). Thus, the development of CIA in DBA/1 mice is influenced by a number of environmental factors, as for RA.

A comparison with previously identified loci that have been associated with autoimmune disease models revealed some striking homologies, especially with arthritis models (Fig. 4). The Cia6 locus on chromosome 6 is homologous with a region on rat chromosome 4 that harbors susceptibility loci for CIA (Cia3) (9), mycobacteria-induced arthritis (Aia3) (10), and pristane-induced arthritis (Pia5 and Pia35) (12). The homologous region in the rat in fact contain two separate QTL controlling pristane-induced arthritis (Pia5 and Pia2) located approximately at the same positions as the two linkage peak in the chromosome 6 region in the mouse (12). In addition, this region appears to contain rat loci associated with lymphopenia (lyp1), diabetes (Iddl) (39), and thyroiditis (40). In the mouse, loci associated with diabetes (Iddd) (41, 42) and lupus (Llw4) (43) have been identified on chromosome 6 although these are more distally located. Taken together, this chromosomal region most likely contains one or several genes of general importance for autoimmune disease. The region contains several interesting candidate genes such as the Igk gene family (Ig κ chain family), Il12a, Il7r, Il5a, and Tcrb gene families (TCR-β).

The suggestive loci on chromosome 10 (Cia8) is homologous with a region on rat chromosome 7 containing the Cia4 locus associated with CIA in the rat. The region contains several collagen genes such as Col10a1, Col8a1, Col6a1, and Col6a2 (procollagen type gene families). The suggestive locus on chromosome 7 (Cia7) is located in a region homologous with a region on rat chromosome 1 that contains the Cia2 locus as well as candidate genes such as Il4ra and the mouse homologue of rat rtk6. The presently identified loci, together with the previously isolated Cia1 and Cia5 associated with mouse CIA, correspond to most thus far identified loci in the rat that show significant linkage with CIA (Cia1–7) (9, 44), suggesting a striking similarity in the genetic control of the disease in both species. Interestingly, in both species, the disease was induced with heterologous type II collagen producing a disease with a more self-limited disease course than the disease induced with homologous CII. However, the finding that at least two of the loci (Cia1 and Cia5) were detected in another more chronic arthritis model, the pristane-induced arthritis (12), indicates that the responsible genes may have general importance for the development of arthritis.

The mouse is a preferred species for the further work to isolate the genes responsible for CIA not only by providing a more economical approach for the production of congenic strains but also by offering the possibilities of using embryonic stem cell techniques. A parallel identification of the genes in mice and rats will provide the best information for further understanding of the basic mechanisms behind autoimmune arthritis and should also ultimately allow the identification of polymorphic genes in humans of importance for RA.

Acknowledgments
We thank Niklas Nordquist, Hamid Darban, and Carl Induss for technical support; Lennart Lindström and Carlos Palestro for animal care; and Drs. Joe Terwilliger and Andrew Cook for advice and critical reading of the manuscript.

References


