Resolution of a 16.8-Mb Autoimmunity-Regulating Rat Chromosome 4 Region into Multiple Encephalomyelitis Quantitative Trait Loci and Evidence for Epistasis

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Resolution of a 16.8-Mb Autoimmunity-Regulating Rat Chromosome 4 Region into Multiple Encephalomyelitis Quantitative Trait Loci and Evidence for Epistasis

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To investigate effects of a 16.8-Mb region on rat chromosome 4q42–43 on encephalomyelitis, we performed a high-resolution mapping using a 10th generation advanced intercross line between the susceptible DA strain and the MHC identical but resistant PVG.1AV1 strain. Clinical signs of myelin oligodendrocyte glycoprotein-induced experimental autoimmune encephalomyelitis (EAE) developed in 29% of 772 F10 rats. Three regions controlling disease, Eae20, Eae21, and Eae22, were mapped using 15 microsatellite markers spanning 16.8 Mb. Eae20 was a major genetic determinant within the region whereas Eae21 modified disease severity. Eae22 was identified as an epistatic region because it only displayed an effect together with Piebald Virol Glaxo (PVG) alleles on Eae20. Disease down-regulation by PVG alleles in the telomeric part of Eae20 was also demonstrated in DA rats made congenic for a ∼1.44-Mb chromosomal region from PVG. As the region containing Eae20–Eae22 also regulates arthritis, together with the fact that the syntenic mouse 6F2–F3 region regulates experimental lupus and diabetes, and the syntenic human 12p13.31–13.2 region regulates multiple sclerosis and rheumatoid arthritis, the present data point to genes that control several inflammatory diseases. The pairscan analyses of interaction, which here identified Eae22, are novel in the encephalomyelitis field and of importance in the design of further studies of this region in other diseases and species. The limited number of genes identified in Eae20, Eae21, and Eae22 enables focused examination of their relevance in mechanistic animal studies and screening of their association to human diseases. The Journal of Immunology, 2005, 174: 918–924.

Common chronic inflammatory diseases such as multiple sclerosis (MS), rheumatoid arthritis, and type-I diabetes (insulin-dependent diabetes mellitus) are complex disorders determined by multiple genes and environmental factors. Identification of underlying genes may provide new strategies for therapy and disease prevention. Although HLA class II genes have an established influence on disease (1–3), the non-HLA genes have largely escaped detection mainly due to genetic heterogeneity and underpowered human studies. Epistatic interactions, in which the genotype at one locus affects the phenotypic expression of the genotype at another locus, further complicate genetic dissection of complex chronic inflammatory disorders (4, 5). These obstacles may be circumvented by genetic dissection of experimental diseases in the inbred dark Agouti (DA) rat strain, which provides highly reproducible models for several chronic inflammatory diseases, including experimental autoimmune encephalomyelitis (EAE) (6) and arthritis (7). A large number of disease-predisposing genetic loci have been identified in F2 and backcrosses between DA and various resistant strains (8–18), and we previously noted a striking accumulation of quantitative trait loci (QTLs) on rat chromosome 4 (19). Of particular interest is a 16.8-Mb region that is linked to experimental encephalomyelitis (8) and arthritis (11, 15, 17, 20) and for which disease regulation is reported in a congenic DA strain that carries a ∼10-Mb chromosomal region (C4R3) from disease-resistant Piebald Virol Glaxo (PVG) (19, 21, 22). Interestingly, although the C4R3 genotype down-regulates several rat models of rheumatoid arthritis, it exacerbates myelin oligodendrocyte glycoprotein (MOG)-induced EAE (21). This model is characterized by both pathogenic T and B cell responses, focal inflammatory infiltrates, and demyelination, and closely mimics MS (23, 24). Apart from regulation of clinical MOG-EAE, the C4R3 genotype influences the anti-MOG Ab levels of the IgG1 isotype, demonstrating a qualitative effect on the autoimmune response (8, 21).

A high-resolution mapping of MOG-EAE was performed in an advanced intercross line (AIL), which allows the separation of closely situated QTLs as well as detection of gene-gene interactions using a pairscan analysis (25–28). These interactions may be lost during fine mapping in congenic strains, because their genomic positioning is highly unpredictable, and they can give inconclusive net effects when contained within the same congenic fragment. Mapping in 772 F10 rats from an AIL between DA and PVG.1AV1 identified two closely situated QTLs within C4R3,
The F2 generation was produced from seven couples each of F1 rats with ical signs for hind leg paralysis or hemiparalysis; 4, tetraplegia or moribund; and 5, tail weakness or tail paralysis; 2, hind leg paraparesis or hemiparesis; 3, (p.i.). The clinical scoring scale was as follows: 0, no clinical signs of EAE; from days 7 to 10 until the day of sacrifice at days 31–38 postimmunization (Aldrich). Rats were weighed and monitored daily for clinical signs of EAE, containing rMOG (20

<table>
<thead>
<tr>
<th>QTL</th>
<th>WL8</th>
<th>MAX</th>
<th>INC</th>
<th>ONS</th>
<th>CUM</th>
<th>DUR</th>
<th>Peak Marker</th>
<th>Genomic Location (Mb)</th>
<th>Syntetic Human Location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eae20</td>
<td>6.7</td>
<td>4.7</td>
<td>7.8</td>
<td>7.2</td>
<td>(2.1)</td>
<td>(3.6)</td>
<td>D4Mgh10</td>
<td>159.4</td>
<td>12p13.31</td>
</tr>
<tr>
<td>Eae21</td>
<td>6.2</td>
<td>4.7</td>
<td>6.4</td>
<td>6.2</td>
<td>3.1</td>
<td>3.9</td>
<td>D4Got131</td>
<td>162.5</td>
<td>12p13.31</td>
</tr>
</tbody>
</table>

* LOD scores and thresholds were generated with R/qtl (25) using the Haley-Knott regression. The thresholds for significant linkage, generated with permutations analysis (n = 1000), were 2.2 for incidence and onset of EAE; and 2.1 for weight loss, cumulative EAE score, maximum EAE score; and duration of EAE.

** The LOD scores in parentheses indicate that the LOD curve did not peak at the specified genomic location, but it is rather significant due to the proximity of the other QTL.

Phenotype abbreviations: WL8, weight loss; INC, disease incidence; MAX, maximum EAE score; CUM, cumulative EAE score; DUR, duration of the disease; ONS, onset of the disease.

* The genomic location of the peak marker and the syntetic human genomic region were extracted from the Ensemble genome database (www.ensembl.org).

Eae20 and Eae21. In addition, we identified another QTL, Eae22, situated telomeric to the C4R3 region, which interacts with Eae20. Experimental demonstration of gene interactions in EAE also has implications for the analysis of other inflammatory diseases linked to this region and syntenic human and mouse regions. Using the congenic strain designated C4R11, which carries a ~1.44-Mb insertion from PVG that is included in Eae20, we demonstrated down-regulation of incidence and severity of encephalomyelitis by the same interval that regulates oil-induced arthritis, Oiu2 (22). Based on the limited set of genes present in C4R11, Eae20, Eae21, and Eae22, we herein discuss mechanisms of disease regulation and gene interactions.

Materials and Methods

Rats

Inbred DA and MHC-identical PVG.1AV1 rats originally obtained from Zentralinstitut für Versuchstierzucht (Hannover, Germany) were used to establish an F0 AIL. In brief, two pairs of DA female founders and two pairs of PVG.1AV1 female founders were bred to create the F1 generation. The F1 generation was produced from seven couples each of F1 rats with DA and PVG.1AV1 as female founders, respectively. The F1 generation originated from 50 breeding couples with both types of female founders. Random breeding of 50 males and females, consistently avoiding brother-sister mating, produced all subsequent generations. Thereafter, three F10 litters were produced for MOG-EAE experiments. The congenic DA.C4R3(PVG) strain was established by selective breeding transferring PVG alleles in the interval between D4Rat63 and D4Rat203 onto DA background (19, 21). All rats were bred and kept at the Karolinska Hospital (Stockholm, Sweden) in a 12-h light/dark cycle, housed in polystyrene cages containing aspen wood shavings, with free access to water and standard rodent chow. They were routinely monitored for specific pathogens according to a health-monitoring program for rats at the National Veterinary Institute (Uppsala, Sweden). Experiments were approved by the local ethical committee in northern Stockholm.

Induction and determination of disease phenotypes

Recombinant rat MOG (aa 1–125 from the N terminus) was expressed in Escherichia coli and purified to homogeneity by chelate chromatography as previously described (29). Age-matched rats between 8 and 16 wk of age were anesthetized with isoflurane (Forene; Abbott) and immunized by a single s.c. injection in the dorsal base of the tail with 200 μl of inoculum containing rMOG (20 μg per rat) in saline emulsified (1:1) with IFA (Sigma-Aldrich). Rats were weighed and monitored daily for clinical signs of EAE, from days 7 to 10 until the day of sacrifice at days 31–38 postimmunization (p.i.). The clinical scoring scale was as follows: 0, no clinical signs of EAE; 1, tail weakness or tail paralysis; 2, hind leg paraparesis or hemiparesis; 3, hind leg paralysis or hemiparesis; 4, tetraplegia or moribund; and 5, death. The following clinical parameters were used: EAE incidence, clinical signs for >1 day; onset of EAE, the first day clinical signs were observed; maximum EAE score, the highest clinical score observed during disease; cumulative EAE score, the sum of all daily clinical scores; duration of EAE, the number of days with EAE; and weight loss (WL8) is a quantitative trait considered to correlate well with a clinical EAE course and that represents (weight at day 8 p.i. – minimum weight during the experiment)/weight at day 8 p.i.

Genotyping and linkage analysis

Genotyping of 794 F10 animals was performed on DNA extracted from the tail/ear tip according to a standard protocol (30). The region analyzed in the AIL covered the transferred congenic C4R3 region and flanking markers (see Fig. 1). The 11.4-cM (16.8-Mb) region, extending from D4Rat137 to D4Rat68 was genotyped with 15 microsatellite markers (Prolog). PCR amplification was performed as previously described (31) with [γ-32P]ATP end-labeling of the forward primer. The PCR products were size fractionated on 6% polyacrylamide gels and visualized by autoradiography. All genotypes were evaluated manually and double-checked.

The linkage map was created using the marker order defined from the publicly available rat genome sequence (www.ensembl.org). All phenotypes were analyzed using the Haley-Knott multiple regression method.

FIGURE 1. Log-likelihood plot showing two MOG-EAE regulating QTLs identified within the 16.8-Mb region using an F10 (DA × PVG.1AV1) AIL. The solid horizontal bars represent transferred genomic regions in the C4R3 and C4R11 congenic strains, and the dotted line extensions represent regions with undetermined genotype. LOD values were determined using R/qtl software (25) for different disease phenotypes: weight loss (thin dotted line), incidence of EAE (thick centered line), onset of EAE (thick centered line), maximum EAE score (thick line), duration of EAE (thin dashed line), and cumulative EAE score (thick dashed line). Eae20 peaked at marker D4Mgh10 and displayed linkage to weight loss, incidence of EAE, maximum EAE score, and onset of EAE. Eae21 peaked at marker D4Got131 and displayed linkage to weight loss, maximum EAE score, cumulative EAE score, and duration of EAE. Microsatellite markers are listed on the x-axis, with peak markers for Eae20, Eae21, and Eae22 indicated in bold text.
Nonparametric point-wise analyses (Fisher’s exact test and Kruskal-Wallis ranking test) were used to confirm the results (JMP version 4.0.2; SAS Institute), but we present regression method data because the same method is required for the multiple QTL model analysis. Threshold levels for significant linkage were determined by a permutation test procedure, which is empirical and reflects the characteristics of the particular experiment to which it is applied (32). Interactions were tested for by implementing a two-dimensional scan with a two-QTL model using the Haley-Knott multiple regression method. Confirmation of QTLs and interactions were done using a fit multiple QTL model test, which analyzes variance using the imputation method for missing genotypes. All computations were performed using R/qtl software (25).

Results

High-resolution mapping of C4R3 in F10(DA × PVG.1AV1) AIL identifies two QTLs

In 772 F10(DA × PVG.1AV1) rats subjected to MOG-EAE, the disease incidence was 29% (223/772), affecting more females than males (150:73), and with clinical characteristics similar to previous descriptions of MOG-EAE in rats (23, 24). In brief, rats developed a first attack of EAE from day 9 and onwards, with initial loss of tail tonus and progression to different degrees of neurological deficits and with different disease courses, including monophasic, relapsing-remitting, and chronic progressive EAE. A 16.8-Mb region, including the C4R3 and flanking regions defined by the markers D4Rat137 and D4Rat68, was genotyped with 15 microsatellite markers in 794 F10 rats (428 females and 366 males) corresponding to the 772 clinically monitored rats and 22 additional rats for which clinical data could not be obtained due to death after anesthesia or too early weaning. Subsequent linkage and permutation analyses with the R/qtl software (25) identified what appeared to be two EAE-linked QTLs located 3.1 Mb apart. The two QTLs were confirmed by the fit multiple QTL model analysis. Eae20 shows maximum base 10 logarithm of the likelihood ratio (LOD) scores for weight loss, maximum EAE score, incidence and onset of EAE at D4Mgh10 (Table I, Fig. 1). However, the LOD score curves for cumulative EAE score and duration of EAE did not form a distinct peak at this genomic location (Fig. 1). This probably reflects influence from the linkage of Eae21 to these phenotypes (Table I, Fig. 1). Eae21 displays maximum LOD scores for weight loss, maximum EAE score, cumulative EAE score, and duration of EAE at D4Got131 (Table I, Fig. 1). For Eae21, linkage to incidence and onset of EAE did not display a distinct peak despite high LOD score values, which probably reflects influence from the linkage of Eae20 to these phenotypes (Fig. 1).

![FIGURE 2.](http://www.jimmunol.org/) a. The significance of epistatic interaction between Eae20 and Eae22. The 16.8-Mb region was analyzed using a two-QTL model that scans for the existence of two QTLs (R/qtl software) (25). The thresholds, generated with permutations analysis (n = 1000), are given in parentheses under the obtained LOD scores. Phenotype abbreviations: WL8, weight loss; INC, disease incidence; MAX, maximum EAE score; CUM, cumulative EAE score; DUR, duration of the disease; ONS, onset of the disease; EPI, epistatic interaction; ADD, additive effect.

b. Interaction analysis in the 16.8-Mb region illustrated by a log-likelihood plot. Interaction analysis was performed using a two-dimensional scan with a two-QTL model. This is a simultaneous search for pairs of interacting loci, which tests all pairs of genomic locations for association with the trait. Interaction data for cumulative EAE score are presented as a matrix [genomic position × genomic position] where the lower and upper triangles represent the additive and epistatic LOD scores, respectively. The bright red area represents high LOD score values resulting from the interaction between D4Mgh10 and D4Got135. Microsatellite markers were plotted on the x- and y-axes. Color codes for LOD scores for both triangles are given in the scale to the right of the matrix. c. An effect plot illustrating the influence of the interaction between Eae20 and Eae22 on cumulative EAE. Rats with a DA allele at D4Mgh10 (Eae20) display a mean value of 10 in cumulative EAE score, whereas rats homozygous for the protective PVG allele at D4Mgh10 (Eae20) and simultaneously homozygous for the DA allele at D4Got135 (Eae22) display a 2-fold higher mean value (D, DA allele; P, PVG allele).
Evidence for QTL interactions and definition of a third QTL

The possibility of QTL interactions was investigated using a two-QTL model that examines all pairs of genetic markers and interactions between them (present model: y = Eae20 + Eae21 + Eae20:Eae21). Thus, the fit multiple QTL model (R/qtl software) (25) based on the comparison between the model of phenotypic variance, which comprises all identified QTLs and interactions between them (present model: y = Eae20 + Eae21 + Eae20:Eae22) and the models from which each component (Eae20, Eae21, or Eae20:Eae22) is excluded. The significant difference (p < 0.05) between the influence on phenotypic variance caused by all components and the influence when one of those components has been excluded, confirms the relevance of the excluded component. Phenotype abbreviations: WL8, weight loss; INC, disease incidence; MAX, maximum EAE score; CUM, cumulative EAE score; DUR, duration of the disease; ONS, onset of the disease.

Characterization of the QTL structure

To confirm the identified QTLs and interactions, we implemented a fit multiple QTL model (R/qtl software) (25) based on the creation of an initial model of phenotypic variance comprising all identified QTLs and their interactions (y = Eae20 + Eae21 + Eae20:Eae22). Each QTL or QTL combination is then excluded from the initial model in subsequent steps, and the resulting influence on phenotypic variance is determined. When comparing the y = Eae20 + Eae21 + Eae20:Eae22 model with a model in which Eae20 is excluded (Table II), a major influence of Eae20 was demonstrated for all EAE phenotypes. Excluding Eae20 revealed influence of this QTL on weight loss, maximum EAE score, cumulative EAE score, and duration of EAE (Table II). Exclusion of the Eae20:Eae22 interaction revealed an influence from this interaction on all phenotypes (Table II). Thus, the fit multiple QTL model analysis confirms that Eae20, Eae21, and Eae20:Eae22 epistasis regulates EAE phenotypes.

Confirmation of MOG-EAE regulation using a congenic strain

For congenic mapping of experimental arthritis, we had previously developed the congenic strain C4R11, which carries a ~1.44-Mb region on 4q42 that was transferred from PVG to DA, and which is included in the Eae20 QTL. Two experiments were performed to determine whether this region regulates MOG-EAE (Table III). Disease in the DA rats was mild and not fully penetrant in the first experiment, whereas it affected all DA rats and caused death in the second experiment. The C4R11 rats were less affected than the DA rats in both experiments, with no sex-associated differences. In the first experiment, the incidence was lower in the C4R11 rats (10%, 2/19) compared with the DA rats (60%, 12/20). In the second experiment, mean maximum EAE and cumulative EAE scores were lower in the C4R11 rats (3 and 55) than in the DA rats (4 and 90), and with lower mortality rates in the C4R11 rats (24%, 5/21) compared with the DA rats (61%, 14/23). Thus, the C4R11 fragment confers disease protection in MOG-EAE (Table III), as it also does in oil-induced arthritis (22).

Discussion

We investigated the genetic regulation of MOG-EAE by a 16.8-Mb region on rat chromosome 4 that colocalizes with QTLs regulating several experimental autoimmune diseases, i.e., Eae20, Eae21, Eae22, Pia7, Cia13, and Ciaa4 (8, 11, 15, 17, 19–21). Using an AIL, we identified two adjacent QTLs, Eae20 and Eae21, which

Table II. Evidence for regulation of MOG-EAE by Eae20 and Eae21 and by the interaction between Eae20 and Eae22

<table>
<thead>
<tr>
<th>Phenotypes regulated by</th>
<th>Eae20 + Eae21 + Eae20:Eae22</th>
<th>Drop Eae20c,d</th>
<th>Drop Eae21</th>
<th>Drop Eae20:Eae22c,d</th>
</tr>
</thead>
<tbody>
<tr>
<td>INC</td>
<td>5 × 10^{-9}</td>
<td>0.0001</td>
<td>0.01</td>
<td>0.001</td>
</tr>
<tr>
<td>ONS</td>
<td>8 × 10^{-9}</td>
<td>0.0001</td>
<td>0.02</td>
<td>0.001</td>
</tr>
<tr>
<td>WL8</td>
<td>3 × 10^{-7}</td>
<td>0.002</td>
<td>0.02</td>
<td>0.001</td>
</tr>
<tr>
<td>MAX</td>
<td>3 × 10^{-7}</td>
<td>0.001</td>
<td>0.02</td>
<td>0.001</td>
</tr>
<tr>
<td>CUM</td>
<td>3 × 10^{-5}</td>
<td>0.001</td>
<td>0.03</td>
<td>0.001</td>
</tr>
<tr>
<td>DUR</td>
<td>2 × 10^{-6}</td>
<td>0.0003</td>
<td>0.06</td>
<td>0.0006</td>
</tr>
</tbody>
</table>

Table III. Clinical MOG-EAE in the C4R11 congenic strain compared with the parental DA rat strain

<table>
<thead>
<tr>
<th>Strain</th>
<th>Incidence (%)</th>
<th>Maximum Score</th>
<th>Cumulative Score</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DA</td>
<td>12/20 (60)</td>
<td>0.8 ± 0.2</td>
<td>2.15 ± 0.58</td>
<td>0/20 (0)</td>
</tr>
<tr>
<td>C4R11</td>
<td>2/19 (10)**</td>
<td>0.6 ± 0.2*</td>
<td>0.79 ± 0.64*</td>
<td>0/19 (0)</td>
</tr>
<tr>
<td>DA</td>
<td>23/23 (100)</td>
<td>4.0 ± 0.2</td>
<td>9.00 ± 6.5</td>
<td>14/23 (61)</td>
</tr>
<tr>
<td>C4R11</td>
<td>21/21 (100)</td>
<td>3.0 ± 0.2**</td>
<td>55.0 ± 6.4***</td>
<td>5/21 (24)*</td>
</tr>
</tbody>
</table>

* Mann-Whitney U test was used to calculate p values for maximum EAE score and cumulative EAE score, and Fisher’s test was used for incidence of EAE and mortality. Significance scores: ***, p < 0.001; **, p < 0.01; *, p < 0.05.

** Maximum and cumulative EAE scores were calculated for affected and unaffected rats and presented as group means with standard errors. Rats that died before the end of the experiment were given score 5, and rats that had to be sacrificed due to severe disease were given score 4.

* Generated by summarizing all daily EAE scores.
independently regulate MOG-EAE. A pairscan analysis of epistatic interactions allowed identification of a third QTL, Eae22, which displays disease regulation only in combination with PVG alleles at Eae20. Epistasis is an important player in the pathogenetics of chronic inflammatory diseases, introducing an additional level of complexity, which is important to address (5). A small region, such as the presently investigated 16.8-Mb region, containing several QTLs involved in complex interactions, could display an undetectable net effect in F2 or backcross populations. This could provide one explanation why Eae20, Eae21, and Eae22 have not been linked to clinical EAE in previous whole-genome scans (8, 9, 33–35).

Eae20 is a major genetic determinant within C4R3, displaying linkage to all encephalomyelitis phenotypes. Using the congenic strain C4R11, which represents a chromosomal interval included in Eae20, we could demonstrate that PVG alleles reduced incidence and severity of encephalomyelitis. The 1.44-Mb C4R11 interval contains a limited number of genes, including a cluster of C-type lectin superfamily members expressed on APCs (Clecsf) (36), a macrophage-specific member of the scavenger receptors (CD163), peroxin 5 (PEX5), and calsyntenin-3 precursor (Clstn3), and possibly the complement components C1R and C1s (Fig. 3) (22). Eae20 also contains additional genes located to the centro-

![FIGURE 3.](http://www.jimmunol.org/)

Eae20 and Eae22 are epistatic, with the telomeric side of C4R3, Eae22 contains the NK cell gene complex (NKC) (Fig. 3), which encodes receptors expressed predominantly by NK cells but also by NK T cells, CD4, CD8, γδ T cells, activated macrophages, and DC. Multiple NKC-encoded receptors are expressed on each cell, and their function depends on the balance of signaling through stimulatory and inhibitory receptors, interacting with diverse ligands. NK cells and NK receptors have been implicated in different autoimmune diseases, and a dual role has been demonstrated in EAE (38–40). The modulatory role could be explained by the identified epistasis, where regulation by NKC depends on the C4R3 genotype (Fig. 3). A similar interaction between stimulatory NKG2D receptor and one of its ligands, RAE-1, has been proposed in diabetes (41). We speculate that Eae20 contains genes(s) that either regulate expression of NK receptors or act as one of their ligands. The molecular mechanisms behind this important regulation event can now be approached.

Impact from multiple QTLs could explain the paradoxical observation that the ~10-Mb C4R3 up-regulates EAE in congenic strains (21), whereas the ~1.44 Mb C4R11 down-regulated EAE (Fig. 3). The disease-promoting influence by the DA allele at Eae20 is sufficiently large to allow disease regulation by this QTL alone, but the protective PVG alleles at Eae20 may predispose to even more severe disease in the presence of the DA alleles at Eae22 (Fig. 2c). This allele combination occurs in the C4R3 congenic strain and might be responsible for the observed disease exacerbation (21). However, the protection conferred by the PVG alleles in the C4R3 congenic strain, which may have the same Eae20:Eae22 allele combination as C4R3, suggests a possible interaction between Eae20 and Eae21 in C4R3 but not in C4R11. This hypothetical interaction between PVG alleles at Eae20 and DA alleles at Eae21 cannot be addressed using the present F10 AIL due to the limited number of rats with that genotype combination. Nonetheless, the observations could be explained by modifier effects from members of the TNFR superfamily in Eae21. We hypothesize that the DA allele in Eae21, when acting independently, displays a disease-predisposing effect, a role assigned in early events of disease induction (42). In C4R11, in the settings of an initiated disease determined by Eae20 and the interaction between Eae20 and Eae22, Eae21 DA alleles might exhibit a beneficial effect through enhancement of removal of pathogenic T cells (43). In the severe disease initiated in C4R3, the
otherwise protective Polygenic Evidence of autoimmune disease susceptibility genes in multiple species will most likely provide insights into the biological processes causing immunemediated diseases.

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References


