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Identification of Quantitative Trait Loci for Susceptibility to Mouse Adenovirus Type 1†

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Adult SJL/J mice are highly susceptible to mouse adenovirus type 1 (MAV-1) infections, whereas other inbred strains, including BALB/cJ, are resistant (K. R. Spindler, L. Fang, M. L. Moore, C. C. Brown, G. N. Hirsch, and A. K. Kajon, J. Virol. 75:12039–12046, 2001). Using congenic mouse strains, we showed that the *H-2*^{s} haplotype of SJL/J mice is not associated with susceptibility to MAV-1. Susceptibility of MAV-1-infected (BALB/cJ × SJL/J)F$_1$ mice was intermediate between that of SJL/J mice and that of BALB/cJ mice, indicating that susceptibility is a genetically controlled quantitative trait. We mapped genetic loci involved in mouse susceptibility to MAV-1 by analysis of 192 backcross progeny in a genome scan with 65 simple sequence length polymorphic markers. A major quantitative trait locus (QTL) was detected on chromosome 15 (Chr 15) with a highly significant logarithm of odds score of 21. The locus on Chr 15 alone accounts for 40% of the total trait variance between susceptible and resistant strains. QTL modeling of the data indicated that there are a number of other QTLs with small effects that together with the major QTL on Chr 15 account for 54% of the trait variance. Identification of the major QTL is the first step in characterizing host genes involved in susceptibility to MAV-1.

Adenoviruses cause 5 to 10% of respiratory illnesses in children and are associated with acute pneumonia in children in developing countries, where the viruses are a major cause of illness and death (21). Five to 15% of pediatric bone marrow transplant patients develop adenovirus infections; morbidity ranges from 50 to 80% (8, 9, 12, 16, 27, 38). However, very little is known about adenovirus pathogenesis, especially contributions of host factors to disease susceptibility. Mouse adenovirus type 1 (MAV-1) provides an excellent model for studying susceptibility to infectious disease because it can be studied in the natural host.

Inbred strains of mice with different susceptibilities to MAV-1 infection have been identified previously (14, 33). SJL/J mice are highly susceptible to MAV-1 infection, with a 50% lethal dose (LD_{50}) more than 4 log units lower than those for other strains of mice, including C3H/HeJ, BALB/cJ, 129/J, and C57BL/6J (33). In vivo studies with immunodeficient mice have demonstrated the importance of innate and adaptive immunity in response to MAV-1 infections. The presence of T cells contributes to immunopathology during the acute phase of infection and to clearance of virus in long-term infection (25). B cell-deficient mice are highly susceptible to MAV-1 infections and die very early, at 6 to 9 days postinfection (p.i.), of a disseminated infection (26). T cell-independent production of neutralizing antiviral immunoglobulin M is a critical factor for control of MAV-1 infection. Infection of primary cells of susceptible and resistant mice ex vivo gives equivalent yields of virus, and sublethal irradiation renders resistant mice susceptible (33). These results suggest that host immune response factors play a role in susceptibility to MAV-1.

We have compared the adaptive immune responses that have been characterized as being important for control of MAV-1 infection (25, 26), as well as NK cell function and induction of cytokines and chemokines by infection, in susceptible and resistant mice (A. Welton and K. Spindler, unpublished data). To date, we have not identified physiological differences between susceptible and resistant strains have been identified by using these approaches. In this report, we show that MAV-1 susceptibility is linked to mouse chromosome 15 (Chr 15) and unlinked to the *H-2* major histocompatibility locus. We used a genomewide search strategy, quantitative trait locus (QTL) detection, to identify host factors associated with susceptibility to MAV-1. This method is advantageous because it does not require prior hypotheses of the pathogenic mechanism and can therefore reveal novel pathways. We measured the susceptibility phenotypes of 192 backcross progeny. The analysis identified a major QTL on distal Chr 15 with a highly significant logarithm of odds (LOD) score of 21.2 and a minor QTL on Chr 5 with a suggestive LOD score of 1.2, based on 5,000 permutations of the mapping analysis. A LOD score of 21 means that the odds are 10^{21}:1 in favor of linkage. The Chr 15 locus alone accounts for 40% of the trait variance

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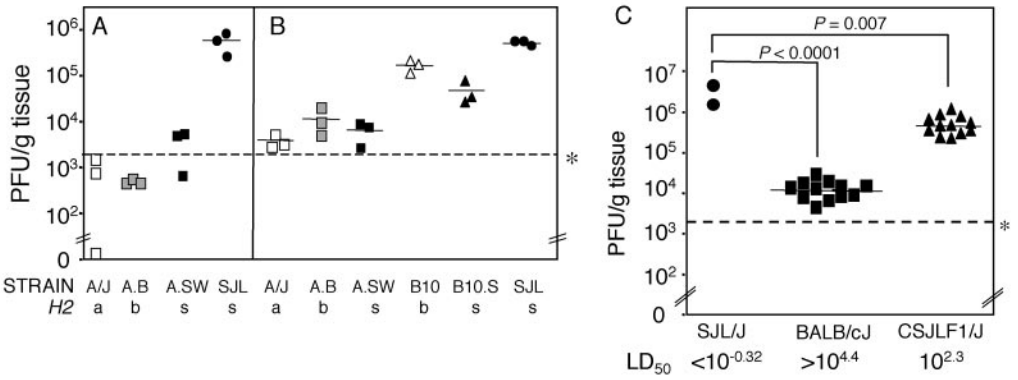

FIG. 1. (A and B) Susceptibility of *H-2* congenic mice to MAV-1. Mice of the indicated strains and *H-2* haplotypes were infected i.p. with 100 PFU of MAV-1. Brains were collected at 8 days p.i., and homogenates were assayed for viral loads via plaque assay. The asterisk and dotted line indicate the detection confidence of the assay; values below this line correspond to fewer than 20 plaques/plate (33). Each symbol represents an individual mouse. Panels A and B show results from independent experiments. (C) Susceptibility of F_1 mice to MAV-1. Brain titers were determined for the indicated parental and F_1 strains. LD_{50}s indicated below panel C for SJL/J and BALB/cJ mice were reported in reference 33 and determined similarly for (BALB/cJ × SJL/J)F_1 mice (CSJLF1/J). Means of the log titers were compared using a two-tailed *t* test, assuming equal variance, and the *P* values are indicated.

between SJL/J and BALB/cJ mice. A single major locus of this influence is readily amenable to positional cloning strategies.

Susceptibility to MAV-1. In LD_{50} assays, SJL/J mice are susceptible to MAV-1 infections whereas mice of other inbred strains, including BALB/cJ, C3H/HeJ, and A/J, are resistant (33). SJL/J mice infected with 100 PFU of MAV-1 have high viral loads in the brain 8 days p.i. ($\sim 5 \times 10^5$ PFU/g), whereas resistant C3H/HeJ mice have low viral loads ($< 2 \times 10^3$ PFU/g). Mice of two additional strains determined to be resistant according to LD_{50}s, A/J and BALB/cJ, also had low viral loads in the brain 8 days p.i. with a dose of 100 PFU (Fig. 1). Because LD_{50} assays cannot be used for mapping studies, in which susceptibilities of individual progeny mice need to be determined, we used brain viral loads as a quantitative measure of virus susceptibility in the studies reported here.

To analyze whether the *H-2*^{s} haplotype of SJL/J mice is associated with MAV-1 susceptibility, we infected congenic mouse strains that differ in their *H-2* haplotypes. A/J mice, resistant to MAV-1, are *H-2*^{a}, and susceptible SJL/J mice are *H-2*^{s}. A.BY-*H2*^{bc} *H2-T18*^{f}/SnJ (A.B) (*H-2*^{b}) and A.SW-*H2*^{s} *H2-T18*^{b}/SnJ (A.SW) (*H-2*^{s}) are two congenic A strain derivatives that we obtained from Jackson Laboratory. We tested these four strains for susceptibility, measuring brain virus loads by plaque assay (7, 33) (Fig. 1A). Mice of strains A/J, A.B, and A.SW did not differ from one another in their virus loads, whereas they did differ from SJL/J mice ($P < 0.002$). Notably, the A.SW and SJL/J mice share the same *H-2*^{s} haplotype and yet had very different viral loads, suggesting that the *H-2*^{s} haplotype does not confer susceptibility to MAV-1. This experiment was repeated with the same strains, and similar results were obtained (Fig. 1B). Also, two additional congenic strains, B10 (*H-2*^{b}) and B10.S (*H-2*^{s}), were tested for virus loads (Fig. 1B). B10 mice had higher viral loads than B10.S mice ($P = 0.023$). These data support the hypothesis that the *H-2* haplotype is not correlated with MAV-1 susceptibility and are consistent with previous findings that the *H-2*^{d} haplotype does not correlate with MAV-1 susceptibility (14). Furthermore, these results were confirmed in the genome scan (see below), in which we found no linkage of susceptibility with Chr 17, the location of the *H-2* locus.

To investigate the inheritance of susceptibility, we tested whether (BALB/cJ × SJL/J)F_1 (CSJLF1/J; Jackson Laboratory) mice were susceptible to MAV-1 by both LD_{50} assay and titration of virus from infected brain homogenates by plaque assay. The LD_{50} of the F_1 mice was $10^{2.3}$ PFU, between that of mice of the BALB/cJ ($>10^{4.4}$) and SJL/J ($10^{-0.32}$) parental strains (Fig. 1C, bottom). The plaque assay results shown at the top of Fig. 1C are similar to results of the LD_{50} assay. The virus load in the F_1 mice was significantly higher than that in mice of the resistant BALB/cJ parent strain ($P < 0.0001$) and was lower than that of mice of the susceptible SJL/J parent strain ($P = 0.007$). These results demonstrate that susceptibility is semidominant and are consistent with its being a quantitative trait.

Antigen capture ELISA for detection of MAV-1 viral particles. Mapping susceptibility to a small genome interval requires analysis of a large number of mice. The size of the QTL interval identified is inversely proportional to the number of recombinant mice generated. The phenotypic assay of susceptibility was the rate-limiting step in our analysis. Therefore, we developed a rapid, reliable, and inexpensive phenotypic screen for viral load, a capture enzyme-linked immunosorbent assay (ELISA) (39), and compared it to our plaque assay method. Briefly, in the ELISA, microtiter plates were coated with rabbit polyclonal anti-MAV-1 antiserum (20), washed, and then blocked with 1% bovine serum albumin. They were then washed and incubated with MAV-1-infected mouse brain homogenates prepared as previously described (33). The plates were washed and then incubated with mouse polyclonal anti-MAV-1 antiserum. The wells were washed, and the mouse antiserum was detected with a horseradish peroxidase-conjugated anti-mouse immunoglobulin G followed by horseradish peroxidase detection and assayed in a microtiter plate reader. ELISA values (optical densities at 450 nm) were calculated by subtracting the mean value for mock-infected brain homogenates, which were considered as background.

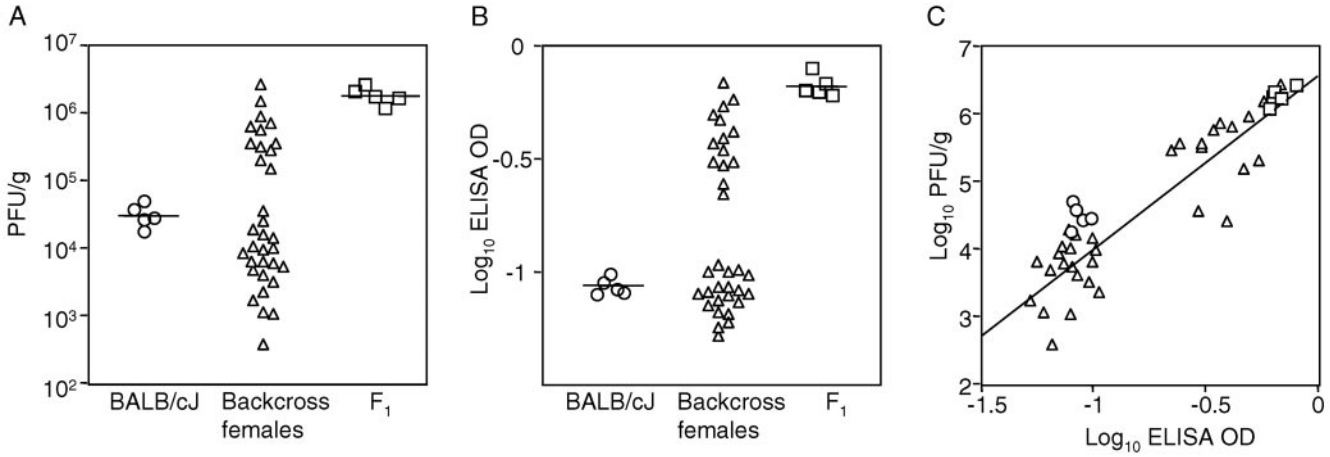

FIG. 2. Backcross mice (3 to 6 weeks old) were infected i.p. with 100 PFU of MAV-1, and brain homogenates were prepared from mice harvested 8 days p.i. Each symbol represents an individual mouse. Circles, BALB/cJ; triangles, backcross mice; squares, F_1 mice. (A) The results of a single plaque assay determination on backcross females and controls are shown. A replicate assay was done on these females, and similar results were obtained (data not shown). Horizontal lines indicate mean values for controls. (B) The results of a capture ELISA on the same mice assayed for panel A are shown. Each mouse brain homogenate was assayed in triplicate, and each symbol represents the average of the triplicate measurements per homogenate. A replicate capture ELISA was done, and similar results were obtained (data not shown). The data were log transformed in order to make statistical comparisons between the plaque assay and capture ELISA methods. OD, optical density. (C) The plaque assay and capture ELISA data from panels A and B were compared in a regression analysis. The line represents the best-fit linear regression.

The capture ELISA and plaque assay methods were used to analyze a small subset of female backcross mice and corresponding parental controls. Plaque assay results are shown in Fig. 2A and capture ELISA results for the same mice are shown in Fig. 2B. We compared the two methods by regression analysis (Fig. 2C). There was a high positive correlation between the results of the plaque assay and those of the capture ELISA ($r^2 = 0.80$). A similar regression analysis was carried out with plaque assay and capture ELISA data on infected male backcross mouse brain homogenates, and the regression again showed an excellent correlation between results of the two assays (data not shown). Therefore, we analyzed subsequent viral loads using the capture ELISA.

Phenotypic characterization of MAV-1 susceptibility in backcross progeny. We investigated the susceptibility phenotype of the progeny of a (BALB/cJ × SJL/J)F_1 × BALB/cJ cross. We set up the backcross with (BALB/cJ × SJL/J)F_1 hybrids as the females because they produce larger and more frequent litters than inbred females (32). The backcross was to BALB/cJ males, because the difference in mean viral loads between F_1 and BALB/cJ mice was greater than that between F_1 and SJL/J mice (Fig. 1C). This allowed optimal discrimination between the phenotypes recovered in the backcross. We analyzed a total of 192 mice (87 females and 105 males), 3 to 6 weeks of age. The susceptibility phenotype was determined using our standard infection conditions of 100 PFU of MAV-1 injected intraperitoneally (i.p.). We then determined the viral loads in brain homogenates at 8 days p.i. by using the capture ELISA. A virus standard was included in each capture ELISA so that assays performed at different times could be normalized. The normalized ELISA data for viral loads in 192 mice were plotted in rank order (Fig. 3). The distribution of phenotypes in backcross mice as measured by viral loads in the brains was consistent with susceptibility being a quantitative trait.

QTL analysis for identification of MAV-1 susceptibility gene loci. To establish chromosomal locations of loci conferring susceptibility to MAV-1, we performed a genome scan on backcross mice. We used 65 simple sequence length polymorphism (SSLP) markers that differentiate between BALB/cJ and SJL/J mice, covering all the mouse chromosomes with an average spacing of 19.1 centimorgans (cM) (supplemental material). BALB/cJ mice had been typed at almost all of these SSLP loci (http://www.informatics.jax.org/), but SJL/J mice had not been as thoroughly characterized. We tested 91 SSLP primer pairs from the database for polymorphism between BALB/cJ and SJL/J mice and used 65 that produced PCR fragments differing in lengths between strains by at least 2 and 8 nucleotides for automated and manual analysis, respectively. We prepared DNA from tail snips of the backcross mice (30). We obtained 12,373 genotypes of a total possible 12,480 (99.14%). Genotypes were distributed as 49.8% homozygotes and 50.2% heterozygotes, not significantly different from the expected 50:50 distribution. There was no evidence of segregation distortion at any individual marker.

QTL analysis involves associating individual genotypes at locations across the genome with a quantitative phenotypic variable, in this case, viral load in the brain as measured by capture ELISA following infection. QTL analysis was performed with R/qtl software, a QTL mapping package for the statistical software R (5). Quantitative trait data for each mouse were entered as the average ELISA (optical density at 450 nm) value of triplicate measurements. These data were then used to determine linkages to genome location across all mouse chromosomes.

An association of susceptibility with markers on Chrs 5 and 15 was observed using the R/qtl imputation method and multilocus models on the data from 192 backcross mice genotyped with 65 markers. A one-way scan for QTLs using the imputation method with 256 imputations on a 5-cM grid (31) showed

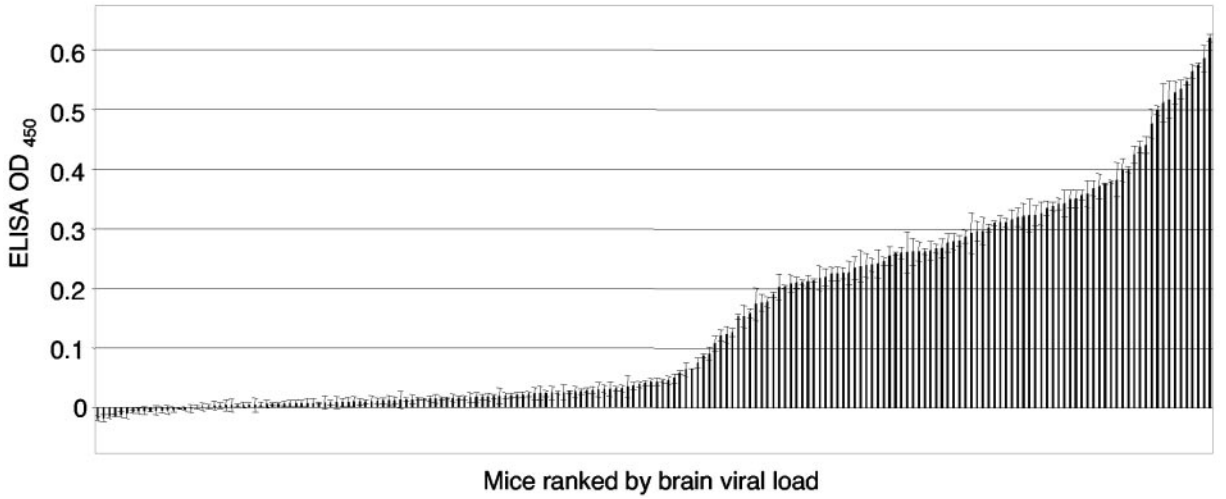

FIG. 3. MAV-1 loads in infected brains of 192 backcross progeny, determined by capture ELISA and plotted in rank order. Each mouse brain homogenate was assayed in triplicate, and each bar represents the average of the triplicate measurements per homogenate. Bars falling below zero indicate homogenate ELISA values for infected mice that were less than uninfected control values. Error bars indicate standard deviation. OD_{450}, optical density at 450 nm.

that viral load was determined by a single major effect QTL on Chr 15 and a small effect modifier on Chr 5 (Fig. 4A). We detected the locus of greatest effect on distal Chr 15 (Fig. 4B). The peak LOD of 21.2 corresponds to 45 cM on the 5-cM grid, between *D15Mit270* and *D15Mit70*. The percentage of variance explained by the QTL on Chr 15 analyzed alone was 39.9% ($F_{[1,\ 190]} = 126.25$, $P = 8.6e^{-23}$). The 2 LOD confidence interval (CI) for the Chr 15 QTL was estimated to be from 39 to 54 cM (based on the map position data in Fig. 4B) from the results of a chromosome-specific scan using an imputed 1-cM grid. This 2 LOD CI corresponds roughly to an interval from ~65 to 78 Mb on the physical map, based on estimation and interpolation from the flanking marker coordinates. The locus on Chr 5 had an additive effect on the phenotype (data not shown). Multiple-QTL modeling analysis of the data using R/qtl (4) indicated that in a model consisting of the loci on Chrs 15 and 5, 41.7% of the trait variance was explained ($F_{[2,\ 189]} = 67.66$, $P = 6.9e^{-23}$).

Interaction of loci affecting MAV-1 susceptibility. The proportion of variance explained by the main effect QTLs on Chrs 15 and 5 (41.7%) implies that there are contributions from environmental factors or other QTLs with small effects. To evaluate the latter possibility, we examined all pairs of loci for additive and two-way epistatic interactions by using R/qtl. Several loci were detected for inclusion in a multilocus QTL model. Because of the very large effect of the locus on Chr 15, additional modifier loci were included in the multilocus model even if they only exhibited a trend toward linkage. Terms were then dropped from this model using backward elimination, with a stay criterion of P of <0.05 for the highest-order term that included any particular factor. We detected an interaction between loci on proximal Chrs 2 and 4 (data not shown). We also examined the influence of sex as both an additive and interacting cofactor and found interactions of sex and genotype at Chrs 4, 8, 13, and 14 (data not shown). Together, the QTLs on Chrs 15 and 5 and these interacting loci accounted for 54.4% of the phenotypic variance. Explanation of >50% of the trait variance by genetic factors is substantial; environmental factors and stochastic and measurement variation are likely to also contribute to the observed trait variance.

Candidate genes for MAV-1 susceptibility. The locus on proximal Chr 15 represents the most significant determinant of MAV-1 susceptibility in the backcross population, contributing 39.9% of the phenotypic variation. The 2 LOD CI from 65 to 78 Mb on Chr 15 includes at least 250 known genes, based on data from Swiss-Prot, TrEMBL, mRNA, and RefSeq databases (found at the University of California—Santa Cruz genome browser site, http://www.genome.ucsc.edu/). Several of the genes between 65 and 78 Mb are of particular interest due to involvement with the immune response. These include the *Ly6* complex, consisting of ~11 gene family members (75 to 76 Mb). The *Ly6* superfamily gene members encode cell surface glycoproteins expressed on discrete hematopoietic populations and are involved in lymphocyte adhesion, T-cell immune responses, and the interferon response (reviewed in references 15 and 29). The heat shock factor 1 gene (*Hsf1*) maps to 77 Mb and encodes the major heat shock transcription factor essential for control of heat shock protein induction in response to environmental stimuli. Mice disrupted for *Hsf1* expression have altered immune and inflammatory responses (18, 40, 41). The Src-like adapter protein 1 gene *(Sla1*) maps to 67 Mb and encodes an adapter protein that regulates T-cell receptor signaling. In the region from 65 to 78 Mb, there are other genes whose functions have not yet been demonstrated that have homologies to genes encoding proteins involved in the immune response, including tyrosine phosphatase and kinase, G-coupled protein receptors, and vacuolar protein-sorting proteins. Fine mapping of the Chr 15 interval using additional recombinant mice and more closely spaced markers will enable us to generate a list of candidate genes that can be tested for correlation with MAV-1 susceptibility. It is possible that fine mapping will reveal that the Chr 15 interval contains two or more QTLs contributing to MAV-1 susceptibility.

There have been a number of studies on mouse susceptibility

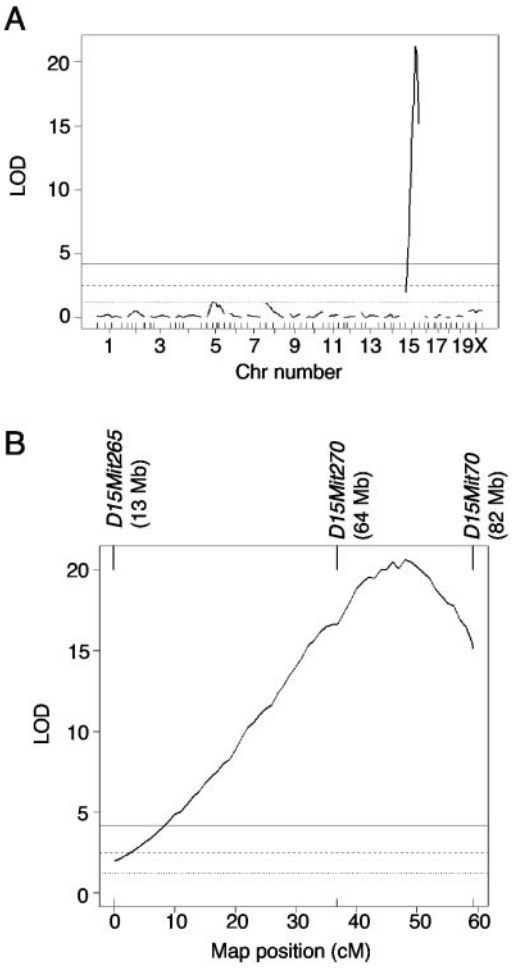

FIG. 4. (A) One-way genomewide scan for QTLs using R/qtl with a 1-cM grid. The analysis is for 192 backcross animals and 65 markers. Tick marks just above the *x* axis represent the 65 SSLP markers used in the genome scan. (B) Interval map for Chr 15 as determined using R/qtl. Note that the map positions indicated are based on the recombination frequencies calculated from the backcross data, and the most proximal Chr 15 marker in our scan, *D15Mit265*, shown at 0 cM, maps to 13 Mb on the physical map. The physical locations of all three markers, based on the Ensembldatabase, release v30.33f (archive date, 22 March 2005; http://apr2005.archive.ensembl.org/Mus_musculus), are indicated at the top in parentheses. The 2 LOD CI for the Chr 15 QTL is from 39 to 54 cM on this interval map, corresponding to ~65 to 78 Mb on the physical map. For both panels A and B, the solid, dashed, and dotted horizontal lines indicate the highly significant ($P < 0.001$), significant ($P < 0.05$), and suggestive ($P < 0.63$) empirical thresholds, respectively, determined by performing 5,000 permutations in the one-way scan.

to animal viruses (reviewed in reference 3), including retroviruses (1, 2, 17, 34), poxviruses (10), polyomaviruses (23, 37), herpesviruses (11), flaviviruses (24, 28), alphaviruses (35, 36), and rhabdoviruses (19). However, the specific genes involved in susceptibility have been identified for only several viruses (6, 13, 22, 24, 28, 36). There have been few studies on susceptibility to human viruses and none on susceptibility to human adenoviruses. Study of the tractable MAV-1 model system has identified one major effect QTL for susceptibility to MAV-1 infection. It is likely that identification of the specific genes involved will provide important insight into mechanisms of virus-host interaction in infectious disease.

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