Letter to the Editor

Genetic variation in the mitogen-activated protein kinase/extracellular signal-regulated kinase pathway affects contact hypersensitivity responses

To the Editor:

Allergic contact dermatitis (ACD) is a T-cell–mediated delayed hypersensitivity reaction characterized by the occurrence of inflammatory skin lesions following contact with a particular allergen.[1] Nonprotein allergens, or haptens, capable of eliciting contact dermatitis include a wide range of substances encountered within occupational or domestic settings.[2] ACD has a reported median prevalence of approximately 20% across Europe and North America and is continuing to increase with limited therapeutic options addressing its burden.[3]

The development of ACD requires an initial sensitization event where cutaneous exposure to a hapten results in an innate immune response. The initial inflammatory response is suppressed by $CD4^+$ regulatory T cells; however, upon a subsequent immune challenge by the same hapten, an inflammatory reaction mediated by $CD8^+$ T cells results in the typical pathology of ACD.[2]

Repeated exposure to haptens has been identified as an occupational risk that can lead to the development of contact dermatitis.[3] However, it is clear that there is variation in individual susceptibility to develop clinically significant allergic reactions. More precisely, susceptibility to the development of ACD is related to the presence of genetic variations such as single nucleotide polymorphisms in genes relevant to this process.[3] Our current knowledge regarding the impact of genetic polymorphisms on contact dermatitis is largely a result of multiple candidate gene–specific studies, with limited whole-genome expression analyses and genome-wide association study approaches.[3,4] Importantly, most previous studies have addressed the genetic susceptibility in sensitization, but the ensuing development of dermatitis has seldom been interrogated. Determining the underlying genetics of the subsequent inflammatory response is of particular relevance, because this is directly responsible for patients' symptoms.

Recently, the development of a large panel of recombinant inbred mouse lines known as the Collaborative Cross (CC) has provided a new model to study complex genetic traits. The genome of each CC strain has been comprehensively characterized and therefore we hypothesized that quantitative trait loci (QTL) can be determined for contact hypersensitivity (CHS) by investigating this particular trait across multiple strains.[5] In this study, we used the CC to investigate the genetic factors underlying CHS, the murine model of ACD in which hapten sensitization and subsequent immune challenge can be fully controlled and standardized.[1,2]

We assessed CHS in 38 strains of CC mice by measuring the increase in ear thickness at various time points after a single standardized oxazalone challenge (see this article's Methods section in the Online Repository at www.jacionline.org). At each time point, there were marked differences in response between CC strains in both the acute response to immune challenge and postchallenge recovery (see Results and Discussion sections and Fig E1 in this article's Online Repository at www.jacionline.org). To determine QTL that control the acute CHS response, we first performed genome-wide linkage analysis on the basis of increase in ear thickness at D1 postchallenge (Fig 1, *A*; see the Methods section in the Online Repository). We identified a major effect QTL on mouse chromosome 4 ($-\text{Log10(P)} = 10.1$) in the interval from 19.7 to 33.1 megabases (Mb) (Fig 1, *B*). Examination of the founder haplotype coefficients through the linked interval on chromosome 4 showed that the causal variant was derived from the 129SlvJ founder strain (hereafter termed 129S) (Fig 1, *C* and *D*).

To determine candidate genes within this interval, DNA variants between susceptible and resistant strains were identified from the Sanger Mouse Genomes database.[6] No 129S-specific missense variants were identified in any gene within this locus; however, a search of the ENCODE database revealed 34 possible 129S-specific regulatory variants affecting 9 coding regions. Of these, *Bach2* was the most plausible biological candidate associated with the observed phenotype (for further discussion, see Results and Discussion sections in the Online Repository). Indeed, we found this causal candidate to be carried by strains within which the most rapid ear-swelling responses were observed. When comparing the SAT strain carrying the 129S haplotype and mounting rapid and intense CHS at D1 to NOD that carried a different haplotype at this locus, we observed a tendency toward reduced regulatory T cells at baseline ($P = .06$) (Fig 1, *G*) and significantly increased IFN-γ–secreting $CD8^+$ T cells in the former (Fig 1, *H*). The strains did not differ in total levels of CD4 or CD8 (Fig 1, *I*). This shows the importance of the $CD8^+$ T-cell response in the phenotype. Of importance, the strains also differed in their macrophage but not neutrophil response, with SAT mice increasing massively the proportion of macrophages (see Fig E2 in this article's Online Repository at www.jacionline.org).

We also mapped a second QTL to chromosome 15 ($-\text{Log10(P)} = 7.8$), in the interval between 32.2 and 55.4Mb, and determined the causal variant to be derived from the CAST founder strain (Fig 1, *E* and *F*). Within this interval we identified *Tnfrsf11b*, *Ebag9*, and *Klf10* as candidate genes, with the CAST haplotype displaying unique noncoding variants of *Klf10* and *Ebag9* within this locus (for further discussion, see Results and Discussion sections in the Online Repository).

We next analyzed the genetic control over the rate of recovery of ear swelling following immune challenge (Fig 2, *A*). Recovery from dermatitis is an important clinical phenomenon because in its absence ACD lesions tend to spread locally and systemically beyond the initial area of contact with the allergen. Remarkably, in several strains the inflammation following immune challenge was maintained over 7 days or worsened despite limiting the challenge to a single application of oxazolone (see Fig E1). We again calculated the genome-wide significance threshold and identified a bifurcated peak on chromosome X that was highly significant ($-\text{Log10(P)} = 17.0$) (Fig 2, *B*) with a 2-logarithm of the odds to the base 10 (LOD) drop between 137.2 and 141.8 Mb. Examination of the founder haplotype coefficients through the linked interval on chromosome X identified that the causal variant was derived from the CAST

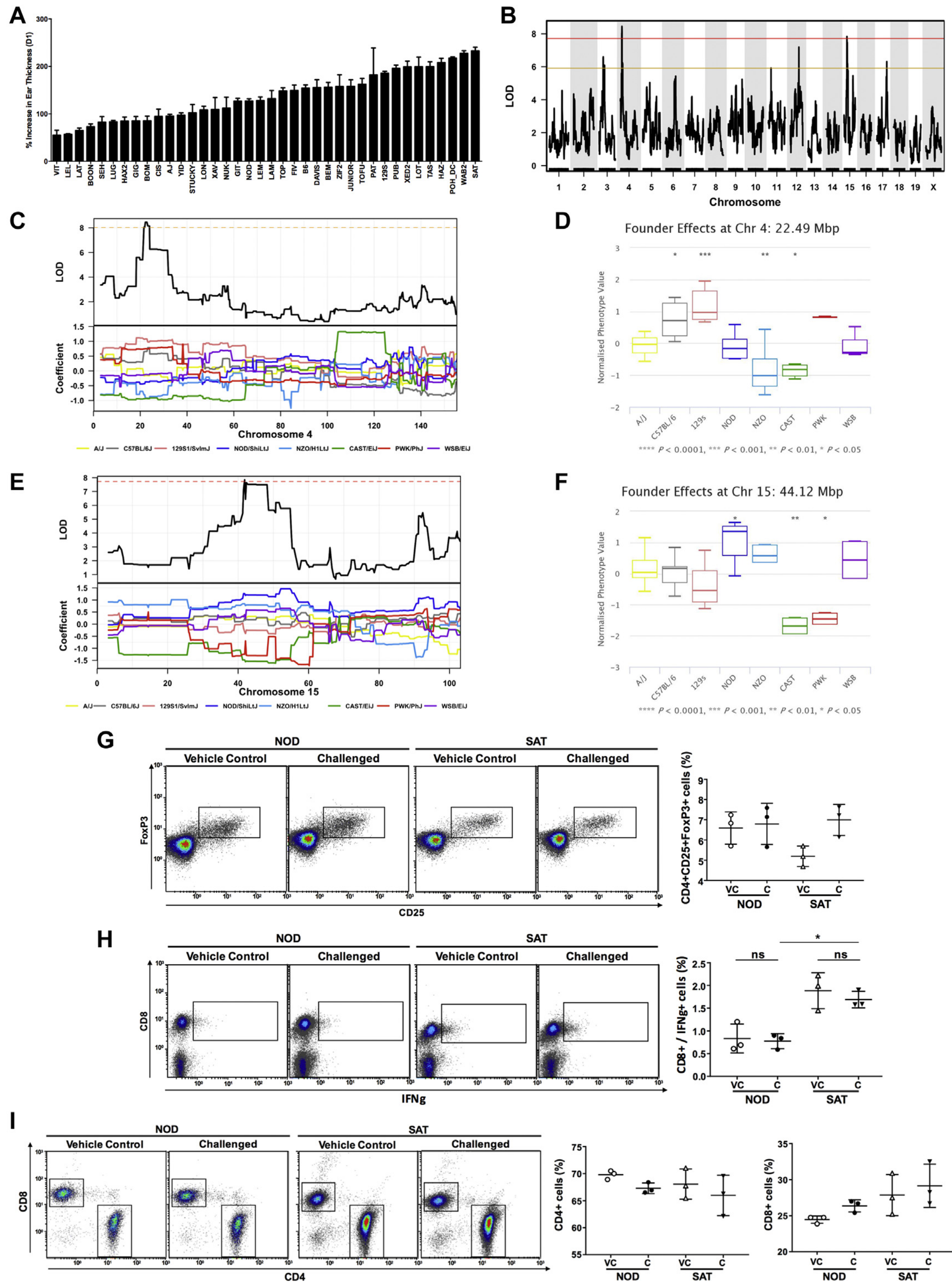

FIG 1. Acute CHS response in CC strains. **A,** CHS response for 38 CC strains (minimum n = 3 per strain, mean ± SEM). **B,** Genome-wide linkage analysis of the acute CHS response identifies a major effect QTL on chromosomes 4 and 15. Horizontal line indicates genome-wide significance threshold based on 10,000 permutations. Red line indicates significance threshold of $P < .01$. **C,** Analysis of founder haplotype coefficients for the identified QTL on chromosome 4. **D,** Statistical analysis of founder effect for the identified QTL on chromosome 4. **E,** Analysis of founder haplotype coefficients for the identified QTL on chromosome 15. **F,** Statistical analysis of founder effect for the identified QTL on chromosome 15. **G,** Flow cytometry analysis of regulatory T cells from cervical draining lymph nodes in challenged ("C") and vehicle control–treated ("VC") NOD and SAT mice (n = 3 NOD, n = 3 SAT mice; mean ± SD). **H,** Flow cytometry analysis of $CD8^{+}IFNg^{+}$ cells from "C" and "VC" NOD and SAT mice. Two-way ANOVA test. $*P = .0295$ (n = 3 NOD, n = 3 SAT mice; mean ± SD). **I,** Flow cytometry analysis of T cells based on CD4 and CD8 from lymph nodes in "C" and "VC" NOD and SAT mice (n = 3 NOD mice; n = 3 SAT mice; mean ± SD). *Chr.*, Chromosome; *LOD*, logarithm of the odds to the base 10; *ns*, not significant.

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