Correspondence

Evidence of a Large- Scale Functional Organization of Mammalian Chromosomes

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The recent report of Shifman et al. [1] challenged one of the findings in our report [2] supporting the concept that the mammalian genome contains blocks of functionally related genes. Among other evidence, we showed that in mice, when allelic combinations in these regions have been disrupted by genetic recombination, the resulting mice have a reduced ability to survive further inbreeding. We also suggested that this was a broader phenomenon based on an apparent genome- wide reduction in survival of recombinants among recombinant inbred lines of mice that have survived a second round of inbreeding.

The failure of Shifman et al. to confirm this latter observation derived from their inclusion of the so-called "new BXD" lines in Table 3 of their paper that served as the basis for calculating the genetic length of recombinant inbred lines. Applying the Haldane-Waddington equation to these mice for calculating genetic distances is not appropriate, because they were developed from an advanced intercross population with a resulting excess of recombinations. Examination of Table 3 confirms this. Shifman et al. have now generously made their initial data available to us; using a revised Table 3 with these lines removed and the same methodology as Shifman et al. generates a map length of 1393 ± 14 cM. This is 14.7% shorter than their estimate of 1630 cM for single meiosis genetic length of the mouse genome (their Table 1); we reported a reduction of 18.1% using different data sets and methodologies.

We have been in communication with the authors of Shifman et al., and they are in agreement that this new formulation of the results is correct.

We conclude that the recalculated results of Shifman et al. now provide additional support for our original conclusions regarding the functional organization of mammalian genomes.

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Evidence of a Large-Scale Functional Organization of Mammalian Chromosomes: Authors' Reply

We agree with Petkov and colleagues that including the BXD lines ("new BXD"), which were derived from advanced intercross lines (AIL), increases the map length in the recombinant inbred (RI) lines. As we note in our paper "One BXD subset was developed using advanced intercross populations and therefore contains approximately 1.7 times more recombinants per line"[1]. If the "new BXD" set were analyzed by itself, an AIL-specific map expansion factor should be applied [2]. However since our motivation was to obtain an accurate estimation of the relative rates of recombination in different regions of the genome, we analyzed all of the RIs together to increase the number of recombination events and the overall density of polymorphic markers. This increased our sensitivity, for example, to identify regions of extremely low and high recombination rates.

There are a number of explanations as to why the map length should differ from that expected on the basis of the Haldane-Waddington equation [3,4].

The estimated map distance of the RIs depends also on the marker density [2] and on the number of inbred generations [5], factors that act to reduce the map length relative to the Haldane-Waddington theoretical equation (which assumes a fully inbred line). It has been hypothesized that "the apparent genetic interference of the accumulated generations (e.g., RIs) differs from the genetic interference acting in each meiosis and that commonly used map functions lead to reduced map distance estimates in the advanced designs" [5]. Consequently, it is not clear that the observed can be explained solely in the way suggested by Petkov et al. ■

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