Letters to the Editor

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Response to Kruglyak

To the Editor:

We accept that our simulations (Sawcer et al. 1997) did not accurately model our experiment in the important respect that extra markers were added after an interim analysis. However, this was not the only respect in which our genome screen differed from the situation that generated the theoretical results discussed in the original paper of Lander and Kruglyak (1995). Kruglyak's recent simulations still differ from our genome screen in important respects: his simulations used uniform markers spaced on a uniform map and involved a genome with chromosomes of a uniform length and families with a uniform pedigree structure. Our simulation study was as much aimed at assessing the importance of these features of real studies. To do this required massive computational effort, and it was simply not feasible for us to include the two-stage aspects at the same time. We should also point out that, in common with most "two-stage" studies, our second-stage study did not simply add extra markers—it added extra families as well. In such circumstances, it is not clear whether the simulations of Kruglyak are quite as relevant, since it will surely no longer be inevitable that the effect of increasing the marker density will almost always be to increase the maximum LOD score (MLS). It would be interesting to see the results of a simulation exercise that also considered the introduction of further families at the second stage. Intuitively, we might expect them to be intermediate between our results and those of Kruglyak.

This aspect of our genome study was one factor that led us to neglect the addition of extra markers. A second was that our general experience has not confirmed the assertion that the effect of adding extra markers is almost always to increase the MLS. We often find the reverse—the initial peaks disappear when additional markers are added! However, we also find Kruglyak's results persuasive. It is well recognized that genotyping and mapping errors tend to reduce the observed MLS (Ott 1991), and it is possible that these account for the discrepancy between our perceptions and the simulation results, since neither set of simulations considered these.

To summarize, we accept that our simulation study oversimplified the conditions of our genome screen in one important respect. But the real study had a number of further difficult aspects, and Kruglyak's simulations also neglect these aspects. We must concede, however, that perhaps we overstated the generality of some of our conclusions. Finally, we would make a plea that this debate should not be concerned solely with the "significance" of a single high MLS. In many cases, it may well be of considerable interest that substantially raised MLSs were found in a number of regions, even though none of them is singly convincing. This is another aspect of the interpretation of genome screens that may be valuably addressed by simulation.

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