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Response to Comment on “Ongoing Adaptive Evolution of *ASPM*, a Brain Size Determinant in *Homo sapiens*” and “*Microcephalin*, a Gene Regulating Brain Size, Continues to Evolve Adaptively in Humans”

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Currat *et al.* present computer simulations to argue that the haplotype structure found at the *microcephalin* and *ASPM* genes can be better explained by demographic history rather than by selection. The demographic models they adopt, however, strongly contradict a decade of empirical research on human demographic history and do not account for the critical features of the data on which our argument for selection was based.

Currat *et al.* (1) argue that the haplotype structures we identified in the human *microcephalin* and *ASPM* genes could be explained by demographic history rather than by selection. To support this claim, they generated simulated data sets to show that some demographic models can produce haplotype structures similar to the ones observed at these loci. That there exist some demographic scenarios that can produce the kind of haplotype structures seen for *microcephalin* and *ASPM* is not surprising. For virtually every signature of selection in population genetics data, one can devise a demographic model that could produce a similar signature. As Currat *et al.* state, however, the question is whether these demographic models are “reasonable.” On the basis of what is known about human evolutionary history, the first model they propose is inconsistent with empirical observations, and the second model ignores the very features of the data that are incompatible with neutral evolution.

Currat *et al.*'s first model posits a history of population subdivision followed by growth. The compatibility of this model with the data from the *microcephalin* and *ASPM* loci requires an extremely narrow and prolonged bottleneck in the subpopulation. A history of structured population bottleneck in the course of human evolution is well established (2) and was consequently incorporated into our own models (3, 4). Currat *et al.*'s model, however, is far more extreme

than, and strongly conflicts with, previous empirical estimates of human population bottleneck based on analyses of both allele mismatch distributions and frequency spectra.

In a large-scale genomic survey, Marth *et al.* (5) analyzed the mismatch distribution of more than 300,000 single-nucleotide polymorphism (SNP) markers to estimate the size and duration of the human structured bottleneck. Their best-fit model estimated a population size reduction to 450 individuals lasting for 800 generations. Studies of allele frequency spectra, based on both several million SNPs and unbiased resequencing data, have estimated a bottleneck range from 500 individuals for 240 generations to 3000 individuals for 1000 generations (6–8). The models proposed by Currat *et al.* (1) are much more severe than these empirical estimates, with the effective population size reduced to 10 to 100 individuals for 1000 generations. The only scenario in which they allow for a realistic bottleneck size (1000 individuals) calls for a highly inflated duration of 5000 generations. Because current empirical estimates are varied, some uncertainty is inherent in any model of human demographic history, but this uncertainty lies within a certain range of acceptable values. In an effort to define this range, Voight *et al.* (9) constructed an acceptance region of the parameter space for models of human demographic history by combining tests of multiple summary statistics. Their estimated range is between 1000 individuals for 400 generations and 4000 individuals for 1600 generations. The parameters in the Currat *et al.* models lie far outside this range.

In their second model (1), Currat *et al.* invoke range expansion, simulating 100 genes

across a stepping-stone grid. However, the authors should have stated that their model ignores recombination, treating each gene as a single-site locus. As such, it tests for a high-frequency allele of a SNP with a specific pattern of population differentiation, not a high-frequency extended haplotype, which was the notable observation that was simulated in our test of selection. The high-frequency haplotypes of *microcephalin* and *ASPM* span across 30 kb and 62 kb, respectively, but Currat *et al.*'s spatial growth model ignores this crucial feature of the data and is consequently inapplicable here. That genetic drift can generate a high-frequency allele with spatial differentiation is not surprising; this is precisely why high values of population differentiation statistics such as F_{st} are only suggestive of selection. Our test of selection was entirely independent of the haplotypes' spatial distributions, which were analyzed simply to elucidate the potential origin of these haplotypes. Furthermore, in our analysis of the haplotypes' spatial distribution, we explicitly stated that the observed frequency variations could be the result of demographic factors. It should also be noted that Currat *et al.* disclose only the fraction of simulations generating a high-frequency allele outside Africa, not those generating a geographic distribution similar to the observed data, making a quantitative assessment of this comparison impossible.

Currat *et al.* (1) state that tests of selection “must first reject reasonable alternative explanations based on demographic models alone.” We agree. If demographic models incorporated into tests of selection are arbitrarily chosen, then the rejection of neutrality as a null-hypothesis becomes arbitrary as well. Where we disagree is in our criteria for a reasonable model. In our view, reasonable models are ones that are compatible with empirical observations. Currat *et al.* arbitrarily chose the minimal demographic parameters that can generate the desired haplotype structure and argue that the resultant model is reasonable on the basis of seemingly qualitative or intuitive terms, without the burden of empirical validation.

The authors' criticism of our choice of demographic models is also a criticism of virtually all studies aimed at identifying recent positive selection in the human genome. These studies all share a similar range of demographic parameters based on the various empirical estimates made over the past decade (10–15). Thus, Currat *et al.*'s demographic models are in contradiction with not only our conclusions, but also the conclusion of many other human population genetics studies in the literature devoted to the identification of selected loci.

In conclusion, we fully encourage the re-examination of demographic models used in our study and others, because the increasing availability of genome-wide variation data will undoubtedly enhance our understanding of human

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demographic history and improve our ability to test for selection. Such reexamination, however, must be consistent, at least to a first approximation, with empirical findings and account for all relevant features of the data. Otherwise, it is simply an exercise in subjective parsimony.

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