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Response to Lohmueller et al.

To the Editor: In this issue, Lohmueller et al. rightly noted that we doubly corrected for unequal male-female population sizes, a mistake that inadvertently perpetuated itself in subsequently derived equations. We are grateful to these authors for pointing out our mistake so quickly and thus helping us to rapidly correct our calculations. We complete the corrections made by Lohmueller et al. in their comment in our Supplemental Data, available online, where we show correct versions of the derived equations and updated resulting figures and tables.

Our mistake led us to underestimate the breeding ratio β. The corrected estimates are greater but still within a range of ratios of the male-to-female reproductive variance encountered in societies characterized as monogamous or serially monogamous, although they also overlap with those characterizing polygyny.[1] Our updated estimates are at the low end of the estimates obtained by Hammer et al., which ranged from 1.8 to 14,[2] and thus do not strongly support the results and conclusions discussed by these authors.

Importantly, in addition to capturing sex differences in the reproductive variance, β can be affected by sex differences in the generation time, by sex-biased migration or inbreeding, as well as by matrilocality or patrilocality and possibly by sex-asymmetric admixture.[3,4] Furthermore, following a population bottleneck, β estimates can be skewed as a result of a faster equilibration of a genetic system of lower effective population size, such as that of the X chromosomes versus the autosomes. Therefore, estimates of β from population-diversity data have to be interpreted in the context of demographic, anthropological, evolutionary, and paleontological evidence.[1,3]

Our estimates of β were derived from the ratio of N_{eX}/N_{eA} estimated from the ratio of the population recombination rates of these chromosomal systems. Lohmueller et al. remarked that N_{eX}/N_{eA} is a more robust statistic than β itself. In addition, focusing first on N_{eX}/N_{eA}, it may be easier to partition the distinct contributions of the factors enumerated above to the overall numeric outcome of this ratio in order to eventually extract only the part influenced by the breeding ratio and use it directly to estimate β. This is, however, conditional on the data and the genetic information that can be used to evaluate distinct contributing parameters. Combining information that can be obtained from historical recombinations[3] with that obtained from mutations[2,4,5] should help this task, both in testing population models and in refining the resulting estimates.

Using our new approach, one can extract additional information from the genetic-variability data to confront different estimates obtained independently from the analysis of the mutational diversity and to examine their consistency. Divergence of such estimates prompts additional investigations. For example, the estimate of about 5 of the ratio, α, of the male-to-female mutation rate,

from Θ_X/Θ_A evaluated by Lohmueller et al. with the use of the CHB and JPT β of 1.4 is consistent with the "phylogenetic" estimate based on the human and ape X chromosome versus autosome divergence[6] (Table S3 and Figure S8). However, estimates of α of up to 22 were obtained with the use of the β estimates at their face value for both CEU and YRI populations. Because values of α of up to 22 are unrealistic, it is plausible that the greater β values found in these two populations are inflated and that other factors additionally influenced the underlying N_{eX}/N_{eA} estimates.[3,4]

Lohmueller et al. implied that α could be estimated solely from the X chromosome versus autosome divergence. This approach works with phylogenetically distant species such that the effect of the common ancestral population size can be neglected. This is not the case in humans and apes.[6] Very divergent species differ in the generation time and in the number of germ cell cycles between the sexes, both influencing α.[5] Therefore, realistic α estimates are expected only when closely related species are considered, which requires correction for the size of their common ancestral population to be made separately for the X chromosome and for the autosomes and thus involves β. Indeed, when applying such a correction by considering a range of ancestral Θ_X/Θ_A to reflect different combinations of β and α, one obtains estimates of α in the range of 5 to 6 (Table S3 and Figure S8). With realistic α, other related estimates should fall in the realistic range, otherwise disproving the model.

In our study, we extended the testing space of genetic models by including the data on historical recombinations. Considering both mutational and recombinational data can enrich historical inferences and even make them more robust. In their comment, Lohmueller et al. not only praised our approach and helped us straiten our equations, but they also positively contributed to the discussion concerning the interpretation of population parameters estimated on the basis of simplified models. These models are essential for improving our understanding of human population history, but their utility depends on careful interpretation and assessment of model assumptions and limitations. This can be best achieved through complementary approaches maximizing the use of all information and through fruitful discussion as exemplified here.

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Supplemental Data

Supplemental Data include a corrected version of Material and Methods text, Appendix A, Figure 1, Figure 2, Tables S1–S3, and Figures S6–S8 and can be found with this article online at http://www.cell.com/AJHG.

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