# Intergenerational mutation rate does not equal long-term evolutionary substitution rate

Recently in PNAS, Langergraber et al. (1) presented interesting findings regarding body size and generation times in chimpanzees and gorillas. The authors then combined these data with recent whole-genome estimates of human mutation rate per generation to recalibrate previous estimates of divergence times in great apes and humans. The authors' divergence estimates are older than previous findings, which reduce the conflict of previous estimates with some contentious older fossil hominins. It is important to have accurate estimations of generation time, but the authors were quick to apply new intergenerational mutation rates to estimates of divergences millions of years ago, without consideration of the issues this has raised in the past (see ref. 2).

Although it is generally accepted that the long-term rate of molecular evolution should equal the rate of neutral mutations over long time scales, this is frequently not observed for short time scales (2). Many biological and methodological factors are likely to affect the time dependency of molecular evolutionary rates, including serial bottlenecks, ancestral polymorphisms, nonneutral mutations, substitution saturation, purifying selection, and demographic parameters (see ref. 2 and references therein). The combination of these factors is thought to result in the apparent increased rate of molecular evolution over shorter time scales. New genomic intergenerational mutation rates are unexpectedly slower than previous long-term rate estimates (e.g., ref. 3), so it is unfortunate that the authors have used these slower intergenerational rates to recalibrate hominid divergence times without any discussion of the effects of biases in the inference of that rate. Some might argue time-dependent rate-curve effects have been solved by using nuclear rather than mitochondrial DNA, but they have been observed in human nuclear DNA studies (2).

Pedigree mutation rates derived from whole-genome sequencing are still in their infancy. Most of these rates currently involve small sample sizes, single populations, or focus on condition-specific studies (autism, schizophrenia, and so forth). Faster rates from larger sample sizes than that used by Langergraber et al. (1) have also been recently published, (for example, ref. 4) and no doubt more estimates will emerge. Appropriate modeling of the uncertainty around these neutral rate estimates is also necessary. It will be some time before an accepted "true" whole-genome single-generation mutation rate is known, if a single rate even exists.

Further complicating the picture, mutation rate and parental age are correlated (5). Therefore, if generation times between species vary, the mean mutation rate will as well. Additionally, it is inappropriate to use human mutation rates for chimpanzees and gorillas, as these species have different demographic histories, particularly in the last few thousand years. As intergenerational data are generated for the great apes, the generation times calculated by Langergraber et al. (1) will be important in improving mutation-rate estimates for great apes. In summary, the data presented on great ape generation time and body mass is both meaningful and interesting; however, the inference of significantly earlier divergence times in the great apes is premature.

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