LETTER

Reply to Gibb and Hills: Divergence times, generation lengths and mutation rates in great apes and humans

In their comment on our recent publication (1), Gibb and Hills (2) raise several issues that we would like to address point by point.

First, Gibb and Hills (2) doubt that intergenerational mutation rates can be applied to date events in the past. This argument is mainly based on the idea that some intergenerational mutations are slightly deleterious and will eventually disappear from the population because of negative selection. We agree that such a process may take place. However, the fraction of deleterious mutations is likely small (see e.g., ref. 3), and their presence would yield even earlier divergence estimates than given in our article (1), thus strengthening our argument for deeper divergence among great apes and humans.

Second, the authors claim that differing demographic histories may lead to different mutation rates on different lineages. Because mutation rate is independent of changes in effective population size under neutrality, such a difference would need to involve selection. If the strength of selection would be changed substantially by changes in effective population sizes, we would expect to observe differences in the rate of nucleotide substitutions between closely related apes and humans. However, the rate of differences of the human genome to gorilla and the chimpanzee genome to gorilla is very similar [1.75% and 1.81%, respectively (4)], with an appreciable part of the differences likely explained by the draft status of the chimpanzee genome compared with the finished sequence of the human genome.

Third, the authors name several other factors that may influence mutation rates. We are unaware of any processes that link the mutation rate to ancestral polymorphisms. Furthermore, given the small amount of differences observed between the genomes of human and the great apes, we fail to see how substitution saturation could have an appreciable effect on the published split-time estimates used in our study.

Fourth, current estimates of intergenerational mutation rate have a wide confidence interval. We agree with the assessment of Gibb and Hills (2) that more study is needed to arrive at a better mean rate. To accommodate uncertainty in these estimates, we used the range of currently published values to recalibrate population split times. The recently published study of mutation rates in dependence of father's age (5) gives a mean generational mutation rate that falls within this range of estimates.

Finally, the authors deem the use of human mutation rates inappropriate for the estimate of split times between human and great apes. We agree that the direct estimation of mutation rates in great apes is necessary and important. However, given that lineage lengths are not substantially different between human, chimpanzee, and gorilla, we currently see no reason to believe that mutation rates are substantially different.

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1 Langergraber KE, et al. (2012) Generation times in wild chimpanzees and gorillas suggest earlier divergence times in great ape and human evolution. *Proc Natl Acad Sci USA* 109(39): 15716–15721.

2 Gibb GC, Hills SFK (2013) Intergenerational mutation rate does not equal long-term evolutionary substitution rate. *Proc Natl Acad Sci USA* 110:E611.

3 Lesecque Y, Keightley PD, Eyre-Walker A (2012) A resolution of the mutation load paradox in humans. *Genetics* 191(4):1321–1330.

4 Scally A, et al. (2012) Insights into hominid evolution from the gorilla genome sequence. *Nature* 483(7388):169–175.

5 Kong A, et al. (2012) Rate of de novo mutations and the importance of father's age to disease risk. *Nature* 488(7412): 471–475.

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