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**Reply to Mendez et al: the ‘extremely ancient’ chromosome that still isn’t**  
Eran Elhaik<sup>1\*</sup>, Tatiana V. Tatarinova<sup>2</sup>, Anatole A. Klyosov<sup>3</sup>, and Dan Graur<sup>4</sup>

<sup>1</sup> Department of Animal and Plant Sciences, University of Sheffield, S10 2TN, UK

<sup>2</sup> Department of Pediatrics, Children's Hospital Los Angeles and Keck School of Medicine, University of Southern California, Los Angeles, CA 90027, USA

<sup>3</sup> The Academy of DNA Genealogy, Newton, MA 02459, USA

<sup>4</sup> Department of Biology & Biochemistry, University of Houston, Houston, TX 77204-5001, USA

Please address all correspondence to [e.elhaik@sheffield.ac.uk](mailto:e.elhaik@sheffield.ac.uk)

Running Title: The ‘extremely ancient’ chromosome that still isn’t

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Earlier this year, we discovered that an extreme age estimate for a Y chromosomal haplotype (237,000–581,000 years ago) by Mendez et al.<sup>1</sup> was based on analytical choices that consistently inflated its value<sup>2</sup>.

As stated in our original criticism,<sup>2</sup> estimating divergence time is not different, in principle, from estimating the time it takes two cars traveling in opposite directions at known speeds to reach a certain distance from each other. The time inferences will be overestimated if the distance between the two cars is overestimated, or if the speed of either car is underestimated. Similarly, a divergence time estimate will seem larger than the actual divergence time if the genetic distances between sequences are overestimated and/or the rates of substitution are underestimated.

Let us consider a very simple estimation model for the time of divergence,

$$t = \frac{d}{2r} \quad (1)$$

where  $t$  is the divergence time,  $d$  is the genetic distance, and  $r$  is the substitution rate per unit time. To overestimate  $t$ , one needs to overestimate  $d$  and/or underestimate  $r$ .  $d$  is usually estimated by dividing the number of differences between two sequences,  $n$ , by the length of the aligned sequences,  $l$ , and correcting for multiple hits and the like

$$d = \frac{n}{2l} \quad (2)$$

$d$  can, thus, be overestimated by either overestimating  $n$  or underestimating  $l$ . The unit time for  $r$  is years. However,  $r$  is often derived from data on number of substitutions per generation.  $r$  can, thus, be overestimated by assuming that the generation time,  $t_g$ , is larger than it really is.

In selecting values for  $d$ ,  $r$ ,  $n$ ,  $l$ , and  $t_g$ , Mendez et al.<sup>1</sup> consistently and without exception chose values that led to overestimating the time of divergence.

In Elhaik et al.<sup>2</sup>, we discussed many such choices. In the following we will focus on two choices left unexplained by Mendez et al.<sup>3</sup>. The first choice concerns the substitution rate used in the calculation of the TMRCA. Using an estimate based on Y-chromosome substitution rate ( $1 \times 10^{-9}$  substitutions per nucleotide per year)<sup>4</sup> we can calculate divergence times of  $43/240,000/10^{-9} \approx 179,000$  years and  $45/180,000/10^{-9} \approx 250,000$  years, for an average of 214,500 years, very similar to the TMRCA obtained using a likelihood-based method: 209,500 (95% CI: 168,000–257,400) years<sup>2</sup>. Not surprisingly, by employing an autosomally derived value of  $0.617 \times 10^{-9}$  as the mutation rate constant,

which is 1.6 times smaller, Mendez et al.<sup>1</sup> obtained a divergence time 1.6 times higher than that estimate of 290,000 to 404,000 years, with an average value of 347,000 years. More appropriate choices would have resulted in a much lower estimate. Mendez et al.<sup>1</sup> other choices, such as the unprecedented 40 years for human generation time, resulted in overestimating the time of divergence by 20-130%.

The second choice concerns the irregular and questionable comparison of mutation numbers based on sequences of unequal lengths. Mendez et al.<sup>3</sup> compared 240,000 bases of the A00 Y-chromosome that contained 43 mutations with 180,000 bases of the A0 Y-chromosome that contained 45 mutations. In other words, they used data from two segments, in which one segment was smaller than the other by about 25%. In response to Mendez et al.'s<sup>3</sup> allegations of “misunderstanding of population genetic theory,” we challenge the authors to come up with one example in the respectable evolutionary literature in which the branches on a phylogenetic tree were estimated by using pairwise distances based on alignments of different lengths. We note, that textbooks in molecular evolution (for example, Graur and Li<sup>6</sup>) contain specific injunctions against such practices.

### **Acknowledgements**

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### **References**

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