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REPLY TO ANNIS ET AL.:

Is quasi-Mendelian mtDNA competition enough to drive transmission of paternal mtDNA?

Jesse Slone[a], Shiyu Luo[b], Paldeep S. Atwal[c], and Taosheng Huang[a,1]

In response to our report of biparental mtDNA inheritance (1), Annis et al. have conducted their own evaluation of our results (2). They disagreed with the autosomal dominant-like inheritance model we proposed as well as the idea of NUMT contamination suggested by others (3, 4). Instead, they offer a mathematical model based on mtDNA dynamics, wherein the paternal mtDNA outcompetes the maternal mtDNA to overcome its numerical disadvantage in the embryo. The phenomenon of competitive differences between mtDNA haplotypes has been previously reported (5). We have previously considered this idea and agree with the idea of a competition mechanism by which paternal mtDNA could contribute to the offspring.

That being said, there must be an additional factor involved in these biparental transmission events. No matter how competitive the paternal mtDNA is, before it can outcompete the maternal mtDNA the paternal mtDNA must "survive" the aggressive elimination of paternal mitochondria from the embryo, which is a major driver of the maternal inheritance of mtDNA. Quasi-Mendelian mtDNA competition and mitochondrial segregation alone will not be sufficient to produce the frequency and pattern of paternal mtDNA transmission in our families, particularly in Family A (1), where the paternal mtDNA transmission occurs multiple times and is vertically transmitted in multiple generations. Thus, the ability of a paternal mtDNA to escape active elimination must be a component of this paternal transmission process. Currently, the mechanism of this "escape" remains under investigation.

Finally, while Annis et al. (2) largely ignore the critiques described in the bioRxiv preprint from Salas et al. (3), we would like to address those criticisms directly here [and in more detail in our Supporting Notes on figshare (6)]. First, Salas et al. (3) clearly state that their reassessment of our raw data shows "strong correlation to the NextGENe results provided by the authors on a per sample base [sic]." In other words, their reanalysis of our raw data reached the same conclusion as ours. However, despite that fact, they proceeded to offer several alternate explanations for our results, including blood sample contamination, bone marrow transplants, in vitro fertilization (IVF), and so on. As stated in our original paper, we have taken extreme cautions to rule out contamination in this study, even going so far as to involve more than one CLIA-accredited laboratory in the process. Additionally, for some cases, no research team members were involved until the data and reports were generated in the clinical laboratory. In the end, all results showed consistent haplotypes and family-specific variants for each individual, as well as the haplotypes being transmitted within each family. It is impossible that these results are due to contaminations or human error. Likewise, the idea that bone marrow transplantation and IVF would have occurred multiple times across all three families while escaping our notice is impossible. We recognize that biparental mtDNA inheritance is an extraordinary claim, and that many unknowns have to be resolved. However, it is impossible for any of the reasons proposed by Salas et al. (3) to explain our observation.

1 S. Luo *et al.*, Biparental inheritance of mitochondrial DNA in humans. *Proc. Natl. Acad. Sci. U.S.A.* **115**, 13039–13044 (2018).
2 S. Annis *et al.*, Quasi-Mendelian paternal inheritance of mitochondrial DNA: A notorious artifact, or anticipated behavior? *Proc. Natl. Acad. Sci. U.S.A.* **116**, 14797–14798 (2019).
3 A. Salas, S. Schönherr, H.-J. Bandelt, A. Gómez-Carballa, H. Weissensteiner, Extraordinary claims require extraordinary evidence in the case of asserted mtDNA biparental inheritance. bioRxiv:10.1101/585752 (25 March 2019).

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Data deposition: Supporting Notes for this reply are available on figshare (DOI: 10.6084/m9.figshare.8236439).
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4 S. Lutz-Bonengel, W. Parson, No further evidence for paternal leakage of mitochondrial DNA in humans yet. *Proc. Natl. Acad. Sci. U.S.A.* **116**, 1821–1822 (2019).
5 J. P. Jenuth, A. C. Peterson, E. A. Shoubridge, Tissue-specific selection for different mtDNA genotypes in heteroplasmic mice. *Nat. Genet.* **16**, 93–95 (1997).
6 J. Slone, S. Luo, P. S. Atwal, T. Huang, Response to Salas et al. (2019) (bioRxiv: 585752), "Extraordinary claims require extraordinary evidence in the case of asserted mtDNA biparental inheritance." figshare, 10.6084/m9.figshare.8236439 (2019).