No further evidence for paternal leakage of mitochondrial DNA in humans yet

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Recently in PNAS, Luo et al. (1) report the observation of heteroplasmic mixtures of mitochondrial DNA (mtDNA) in the blood of three unrelated patients suffering from different mitochondrial disorders. The affected mixed positions coincide with signature mutations of established haplogroups (2), suggesting that each mixture consists of a different pair of distinct and plausible mitotypes. Luo et al. (1) exclude sample mix-up and allochthonous contamination as the source for these observations by engaging two independent laboratories (and even using different sequencing technologies) that confirmed their results on newly drawn blood samples. mtDNA analysis revealed that some individuals in the pedigrees showed the same mixed patterns as the patients, while other individuals exhibited the single-source mitotypes of the respective maternal lineages. Based on these maternal mitotypes, the authors deconvoluted the mixtures observed in the affected family members and deduced the "paternal mitotypes" by reporting the additional, unexplained variants from the maternal mitotypes in a phylogenetically plausible way (see figures 1, 2, and 3 in ref. 1). The authors further conclude that these deduced paternal mitotypes would provide evidence of "biparental mtDNA transmission with an autosomal dominant-like inheritance mode" and propose that "the paternal mtDNA transmission in these families should be accompanied by segregation of a mutation in one nuclear gene involved in paternal mitochondrial elimination" (1). While this line of argument may be a theoretical, albeit highly unlikely, explanation for their findings, their conclusion that it provides evidence for paternal inheritance of mtDNA is not supported by the data. At best, these observations could serve as a hypothesis for additional experiments that include samples from the fathers (or their maternal relatives) to investigate further their claims. However, in the absence of such data, paternal inheritance cannot be asserted.

We suspect that the "autosomal dominant-like inheritance mode" actually derived from nuclear elements of mtDNA (numts) that were coamplified and sequenced together with the genuine mtDNA and thus resulted in the observed mixtures (3). Our main concern is that the authors did not experimentally exclude numts as a possible source for the observed mixtures. This is particularly relevant because the authors used relatively large amounts of DNA (10 ng) for library construction. To exclude numts as the source of the mixtures in the affected individuals, mtDNA-depleted cell lines [i.e., Rho 0 cells (4, 5)] should have been cultivated from, for example, muscle biopsy tissues. mtDNA sequencing of Rho 0 cells should fail to provide mtDNA sequences if paternal inheritance was indeed the source for the observed mixtures. Our concerns are supported by earlier reports that demonstrate the more-recent-than-originally believed insertion of nearly full-length mitogenomes in the nuclear genome (6, 7), thus showing mutational patterns that resemble those of existing haplogroups.

In any case, the experiments presented by Luo et al. (1) are by no means sufficient to even suggest paternal (co)inheritance of mtDNA in humans, because the authors fail to verify their claims by confirming that the deduced mitotypes do in fact match those of the fathers or their maternal relatives.

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