Mitochondrial DNA (mtDNA) sequence variation and maternal inheritance are valuable tools in assessing ancestry of different human populations and for clinical practice. A new study (Wei et al., 2019) reports that the fate of new mtDNA variants in the female germline is non-random as they report functional selection and matching to nuclear ancestry to shape human mtDNA variation.

The majority of cellular DNA resides in the nuclear genome and is inherited equally from both parents. However, mothers contribute slightly more as ~1% of DNA is inherited directly from her via the ~100,000 mitochondrial DNA (mtDNA) copies carried by the egg (Hutchison et al., 1974). But before an oocyte is ready to pass on its mtDNA load to the offspring, it undergoes remarkable mitochondrial remodeling. The mtDNA bottleneck of the early female embryogenesis decreases the mtDNA copy number to <100 copies by an unknown mechanism, after which these mtDNAs are rapidly replicated to reach the hundreds of thousands of copies in the mature oocyte (Shoubridge, 2000). The >1,000-fold increase of mtDNA copies means that a rare variant that survives the bottleneck can become the major mtDNA type in the mature egg and the offspring. By this mechanism the mtDNA genotype can shift within one generation (Figure 1). Furthermore, in addition to the bottleneck, the murine germline selects against deleterious mtDNA mutations (Stewart et al., 2008), adding a further mechanism that defines the final mtDNA content in the egg. In mice, specific somatic tissues undergo selection as well (Battersby et al., 2003; Latorre-Pellicer et al., 2016). The factors that shape human mtDNA variation have, however, been poorly known.

mtDNA encodes only 13 proteins and the ribosomal and transfer RNAs for their protein synthesis (Nunnari and Suomalainen, 2012). Prime quality mtDNA is essential for health, as over 200 mtDNA mutations underlie a variety of human diseases. In disorders, mutant mtDNA often shows heteroplasmy; that is, mutant mtDNA coexists with the wild-type copies in the same cell (Nunnari and Suomalainen, 2012). Until recently, healthy people were assumed to have only identical mtDNA copies (i.e., homoplasmy).

However, in a newly published study, Patrick Chinnery and his coworkers (Wei et al., 2019), utilizing data from the British NIHR BioResource and the 100,000 Genomes Project to study 12,975 whole-genome sequences, including 1,526 mother-offspring pairs, found that almost half showed mtDNA heteroplasmasy at a frequency greater than 1%. These results imply that low-level mtDNA variation is common in the human population.

The inclusion of families in the 100,000 Genome Project gave Wei et al. a unique opportunity to study mother-offspring pairs to explore what kind of mtDNA variants were inherited. They found that new variants were often selected against, whereas previously reported, tolerated ones tended to increase in proportion, suggesting selection against deleterious variants. New mtDNA sequence variants in coding regions and rRNA were under the strictest selection, but also tRNA mutations were selected against, different from the data in mice (Stewart et al., 2008). The data of Wei et al. of essential mitochondrial rRNA sequences, still poorly known in humans, are valuable for interpretation of pathological changes in the context of disease. Altogether, the evidence suggests that mtDNA sequences and the mtDNA replication machinery go through a rigorous testing process during oocyte maturation as these sequences are squeezed through a bottleneck, quality-checked, and replicated 1,000-fold—a true survival of the fittest.

Wei et al. inspected further a heated topic in the mtDNA field. A recent study reported evidence for paternal mtDNA inheritance in three families (Luo et al., 2018). Those findings raised attention, but also concerns, because biparental mtDNA contribution would have major implications for genetic counseling and for timing in evolutionary studies. In their 100,000 Genomes data, Wei et al. identified 196 father-offspring pairs with low-level mtDNA heteroplasmasy. In one of these, the child’s variant was absent in the mother, but present in the father. Despite the variant being common and prone to occur de novo, the finding is compatible with paternal mtDNA transmission. The topic should be revisited in other genome data resources, to establish the frequency of such events. These data highlight the capacity of massive population genome datasets to test and validate experimental data raised from smaller studies.

mtDNA does not work alone. Its 13 protein products assemble with over 90 nuclear-encoded proteins, orchestrated by an army of assembly factors, to generate the functional enzyme complexes of the respiratory chain (Nunnari and Suomalainen, 2012). The tight matching of the subcomponents within the cellular micromachines is essential to prevent premature electron leak and reaction with oxygen, which would generate highly reactive and potentially damaging oxygen radicals. The match is best achieved if the components stem from one type of genome, which may be the reason evolution favored uniparental inheritance in the vast majority of species. In mice, mtDNA variants have been suggested to follow nuclear genome
evolution (Latorre-Pellicer et al., 2016), but no evidence for this process exists in humans. Wei et al. provide exciting data pointing to co-evolution. Again, in their 100,000 Genomes data, they identified cases where mtDNA haplotype and ancestry did not match the nuclear ancestry. For example, if a woman of Asian descent has offspring with a man of European descent, their children’s mtDNA, which used to coexist only with an Asian nuclear genome background, now co-operates in the same cell with European nuclear genome. In this scenario, during subsequent generations, the nuclear genes become increasingly European, but in the maternal line mtDNA remains of Asian origin. Intriguingly, the authors noticed that new mtDNA variants tend to shift toward the nuclear ancestry. The authors propose that the shifting variants often were predicted to have functional effects, raising a possibility that the capacity for ATP synthesis might drive selection. These data suggest that the maternal germline works as a busy match-maker, selecting the mtDNA variants that best interact with their nuclear counterparts.

The report raises important issues for studies utilizing mtDNA variation to assess human population history. To minimize the effect of functional selection, the variants that occur in regions that tolerate changes, preferably synonymous, are the most likely to show linear inheritance. The tendency of mtDNA to shift toward the nuclear ancestry is important to consider when designing mitochondrial transfer therapies, aiming to replace the patient’s mtDNA with healthy donor mtDNA (Craven et al., 2010). The finding supports use of donors with mtDNA haplotype match.

The study also raises questions that remain to be solved. Why is low-level heteroplasmy so common in people? Perhaps it provides a pool of mtDNAs that continuously “probe” potential for evolution and improved nuclear matching. Because of the selective mtDNA bottleneck, beneficial variants could amplify and secure the best mitochondrial respiratory machinery for the offspring (Figure 1). Furthermore, pathological mtDNA mutations do exist, even ones compromising viability soon after birth. How do they leak through the selection?

A few critical points deserve further consideration. Wei et al. extrapolate their conclusions on germline functions from analyzing blood DNA, but they do not discuss the fact that in mice some tissues select for different mtDNA genotypes in a heteroplasmic situation (Battersby et al., 2003; Latorre-Pellicer et al., 2016). In humans, leukocytes are known to select against specific mtDNA variants, such as m.3243A>G (Rahman et al., 2001), which Wei et al. report to show a negative shift. Therefore, the conservative conclusion is that the observed selective forces occur at some point between the female germline and the sampled blood. Hopefully, though, as the extent of tissue bio-banks increases, this question of how representative blood DNA is for other tissues, including the germline, will be addressed.

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REFERENCES


