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Mitochondrial mutation rates in the water flea *Daphnia pulex*

It has long been known that the mitochondrial genome normally mutates at a higher rate than the nuclear genome. Direct estimates of mitochondrial mutation rates can be made by sequencing individuals from mutation-accumulation lines, for which the evolutionary timescale is known exactly. Using such an approach, estimates of mutation rates have been made for a small number of species (e.g. Denver et al. 2000; Haag-Liautard et al. 2008; Howe et al. 2010).

Xu et al. (2012) have estimated mitochondrial mutation rates in the water flea, *Daphnia pulex*, using mutation-accumulation lines. They found no significant difference between the rates in asexual and sexual lineages, which had respective mean rates of 1.37×10^{-7} and 1.73×10^{-7} mutations/site/generation. Assuming a generation time of 10–13 days, these translate into rates of about 4.35×10^{-6} and 5.49×10^{-6} mutations/site/year, respectively. These rate estimates are higher than those from *Caenorhabditis* and *Drosophila*. The 23 observed mutations comprised 17 indels and 6 nucleotide replacements.

As with previous direct estimates of mitochondrial mutation rates, Xu et al. (2012) found that the rates in *Daphnia* greatly exceeded those obtained in phylogenetic studies. For example, their estimates are nearly 400 times higher than the 'standard' evolutionary rate for arthropods (Brower 1994). This disparity in rates has been observed in a range of organisms and can have a substantial impact on the analyses of evolutionary timescales (Howell et al. 2003; Ho and Larson 2006).

The use of next-generation sequencing techniques will enable the production of large datasets for estimating mutation rates. This will improve estimation precision, allowing better characterisation of the patterns and rates of mutation in different species.

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Selection against pathogenic mutations in human mitogenomes

It has long been known that the effects of purifying selection on mitogenomes can be detected at the intraspecific level (e.g. Nachman et al. 1996). Indeed, many mitochondrial mutations in humans are pathogenic and a variety of mitochondrial disorders have been characterised (Taylor and Turnbull 2005). The removal of pathogenic mutations by selection produces a distinctive signature in mitochondrial genealogies, with an excess of deleterious mutations in the younger branches (Nielsen and Weinreich 1999).

By investigating the mutations observed in a large sample of human mitogenomes, Pereira et al. (2011) tested the relationship between the estimated age of each mutation and its estimated functional impact, as measured by a pathogenicity score. Mutation age is estimated using the quantity ρ, which reflects the uncorrected number of mutations separating a given sequence from the putative common ancestor.

The authors find that the pathogenicity score declines with increasing ρ. In addition, mutations that appeared multiple times in the genealogy had a lower estimated functional effect. The authors find similar distributions of pathogenicity scores across the mitochondrial macrohaplogroups L, M and N. Collectively, these findings provide compelling evidence that purifying selection has been acting on human mitogenomes on a global scale, with little difference among major regions of the world.

The authors consider the possibility of changes in population size and structure. If the global human population has become increasingly structured towards the present, this would reduce the effective population size and increase the fixation of non-synonymous (and deleterious) mutations (Chikhi et al. 2010). However, the authors conclude that purifying selection is a more likely explanation for the observed distributions of mutations. The presence of widespread purifying selection has important implications for estimating the mitochondrial timescale of human evolution and dispersal (Endicott et al. 2009; Subramanian 2009).

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Mother's curse: Mitochondria cause problems for male flies

Healthy mitochondria are vital for the fitness of both males and females, but evolution has dealt males a bad hand when it comes to maintaining a good mitochondrial genome. As a general rule, mitochondrial genomes are maternally inherited, so whether you are male or female you will be carrying a copy of your mother's mitochondrial DNA. Males, however, almost never pass on their mitochondrial DNA to the next generation. As a result, male mitochondrial genomes are an evolutionary dead end. Because of this pattern of inheritance, natural selection will operate on the effects that mitochondrial mutations have on females, but it will tend to ignore any effects that those mutations have on males (Frank and Hurst 1996).

If there are mutations that harm males but leave females relatively unaffected (or are even beneficial to females), then males have a problem: natural selection will be very poor at removing these mutations. Because of this, theory predicts that mitochondrial genomes should contain more mutations that harm males than females, an effect known as 'Mother's curse' (Gemmell et al. 2004).

In a recent study, Innocenti et al. (2011) provide compelling evidence that mother's curse operates strongly in the mitogenomes of wild *Drosophila melanogaster*. In a clever set of experiments, the researchers took five naturally occurring variants of *D. melanogaster* mitogenomes and paired each of them with the same nuclear genome. Then they measured the variation in gene expression in the nuclear genomes of both male and female flies. If mother's curse is operating, they expected that there would be

more variations in gene expression in males than in females, and this was exactly what they saw.

Gene expression in females was relatively constant across all five mitochondrial genome variants—expression level varied in only seven of the 11,000 genes tested. In comparison, over 1000 genes varied in expression level in males. This suggests that differences in the natural mitochondrial variants affect males more strongly than females. Furthermore, most of the variable genes in males were expressed in male-specific reproductive tissues, supporting the idea that these genes might directly affect male fitness through changes in fertility. Even more compelling is the fact a significant number of genes that varied in expression level are known to affect male, but not female, fitness (Innocenti and Morrow 2010).

These results provide convincing support for the hypothesis that mitochondria tend to harbour mutations that are more problematic for males than females, at least for wild fruit flies. Intriguingly, a recent addition to the original theory suggests that both inbreeding and kin selection can reduce or even reverse mother's curse (Wade and Brandvain 2009). It would be fascinating to test these theoretical predictions by comparing the strength of mother's curse across species or populations that are known to differ in levels of kin selection and inbreeding, and Innocenti et al. (2011) provide a very neat experimental setup that could be used to do just that.

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