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Distinctive characteristics of post-mortem damage in human mitochondrial DNA

In the past few years, advances in methodology have enabled the large-scale sequencing of mitogenomes from ancient hominids. These have included six Neanderthals and two ancient humans, ranging in age from 4 to 65 kyr. Krause et al. (2010) have recently added to this tally with the publication of a complete mitogenome sequence from an early modern human, dated at 30–33 kyr. The authors employ the primer-extension-capture technique, presented in one of their previous studies of Neanderthals (Briggs et al. 2009), which is able to retrieve sequence fragments as short as 20 nucleotides.

Krause et al. (2010) use an interesting approach to deal with the problem of contamination, which is particularly challenging in studies of human remains. They begin by surveying the characteristics of DNA molecules in a number of Neanderthal samples, focusing on the patterns of post-mortem damage and fragmentation. The authors find three key characteristics of endogenous (authentic) DNA molecules that distinguished them from contaminants.

First, the endogenous molecules are generally shorter, being around 45–60 bp in length. This is an important observation because it demonstrates that PCR-based methods, which usually need to target molecules greater than 50 nucleotides (20 nucleotides for each of the primers and at least 10 nucleotides for the target sequence), are not optimal for studies of ancient human DNA. Second, the feature distinguishing endogenous from contaminant molecules is the much greater presence of C → T changes at the 5′ ends. This type of damage, resulting from the post-mortem deamination of cytosine, was able to be quantified because of the manifold coverage achieved by high-throughput sequencing methods. Third, endogenous DNA molecules show preferential fragmentation at purine bases, whereas this is not the case for contaminant molecules.

Krause et al. (2010) use these features of endogenous molecules to evaluate the authenticity of the sequencing products from the early modern human. They conclude that 98.7% of the DNA fragments from their sample could be attributed to a single individual (presumably the targeted individual). By demonstrating that DNA sequences can be reliably obtained from degraded human samples, the study by Krause et al. (2010) opens the possibility of nuclear genomic sequencing of ancient humans. Indeed, the genomic sequence of an ancient Amerindian is currently in press.

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Time-dependent molecular rates in human mitogenomes

There has been recent attention towards the hypothesis of time-dependent rates, which proposes that estimates of substitution rates are negatively correlated with the observational time-frame (Ho et al. 2005). Several studies have investigated this issue using human mitogenomes, finding evidence for a pattern of declining rates with increasing time depth (for a review, see Endicott et al. 2009). This pattern has been largely attributed to the effects of purifying selection (Endicott and Ho 2008, Soares et al., 2009) and demographic history (Henn et al. 2009).

The latest study of this matter, carried out by Loogväli et al. (2009), involves an analysis of over 3000 mitogenomes from 186 clades. To estimate the age of each of these clades, the authors use a rate calculated from synonymous sites, which appear to exhibit lower levels of time-dependent effects than other portions of the mitochondrial genome. Loogväli et al. (2009) find that younger clades have higher ratios of non-synonymous to synonymous mutations, and higher ratios of RNA to synonymous mutations. In particular, a rapid increase in ratios is observed between 10,000 years ago and the present. These patterns suggest the action of purifying selection over time.

Loogväli et al. (2009) notice that rates at synonymous sites are mildly time dependent, and ascribe this pattern to mutational saturation. However, such an observation can also be explained by the lack of recombination in mitogenomes, which results in the complete linkage of synonymous sites to non-synonymous sites.

A particularly interesting result from the paper is illustrated in Figure 1. As with previous authors, Loogväli et al. (2009) find that the substitution rate of the mitochondrial coding region generally increases as the observational timeframe shrinks; but they depart from previous studies in finding that the increase is not monotonic. A noticeable rise in the substitution rate occurs around 50,000 years before present, coinciding approximately with the dispersal of modern humans out of Africa.

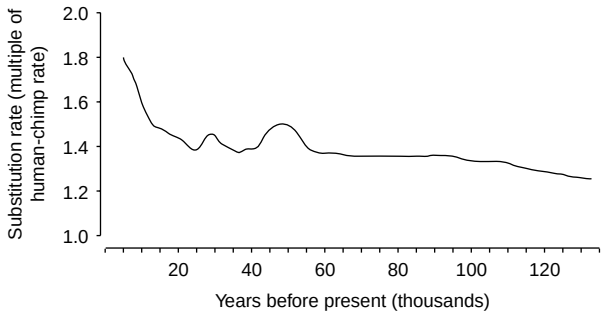

Figure 1. Plot of substitution rate (measured as a multiple of the rate calculated using the human–chimpanzee divergence as a calibration) against years before present. The graph is a cartoon depiction of Figure 3 from Loogväli et al. (2009), which is based on 186 data points.

The study by Loogväli et al. (2009) provides some compelling insights into time-dependent rates and highlights the roles of both purifying selection and population history in influencing substitution rates over time. It will be interesting to see whether these factors have a similar influence on rates in other species. Further understanding of the factors governing time-dependent rates will lead to improved estimates of evolutionary time scales.

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The role of mito-nuclear interactions in F2 hybrid breakdown

Crossing individuals from separate populations can result in offspring (known as F1 hybrids) that are fitter than either of the parent populations. When F1 hybrids interbreed, however, the resultant F2 hybrids tend to have markedly lower fitness—a phenomenon known as F2 hybrid breakdown. This breakdown could be due in part to the interactions between the mitochondrial and nuclear genomes (reviewed in Dowling et al. 2008). These mito-nuclear interactions stem from the fact that the mitochondrial proteome is encoded in both genomes. Because interactions between these proteins are vital for mitochondrial function, one might expect the proteins encoded in the two genomes to co-evolve. This kind of co-evolution could cause problems for F2 hybrids because they may

inherit nuclear and mitochondrial alleles from different populations. Bringing together these separately-evolved regions into a single organism could result in a mitochondrial proteome with poorly interacting subunits.

In a recent study, Ellison and Burton (2010) investigated this hypothesis using the copepod *Tigriopus californicus*. They focus on characterising the inheritance of mitochondrial DNA (mtDNA) and the nuclear-encoded mitochondrial RNA polymerase, mtRPOL, among a number of hybrid crosses. Although there are a vast number of nuclear-encoded mitochondrial proteins, mtRPOL was seen as a likely candidate for involvement in mito-nuclear interactions because of its vital roles in both mitochondrial replication and transcription, and because it had been implicated in a previous study (Ellison and Burton 2008). Ellison and Burton (2010) find that mtDNA copy number in F2 hybrids is highly variable, and that this variability can be partly explained by the mtRPOL genotype. Individuals in which the mtRPOL alleles are derived from a different population from the mtDNA show large deviations in their mtDNA copy number compared with the parental populations. Furthermore, when the mtDNA copy number in F2 hybrids is higher than the parental populations, the hybrids show significant decreases in their ability to respond to osmotic stress.

These results support the hypothesis that mito–nuclear interactions play a significant role in determining the fitness of F2 hybrids. Furthermore, the results generate testable hypotheses with respect to the genes that underlie these interactions. Although the authors focus on the mtRPOL gene, they acknowledge that it is possible their results might also be explained by the inheritance of a closely linked nuclear-encoded mitochondrial protein, mtTFB1. Whatever the respective roles of these two proteins, this study represents a significant advance in tracking down the functional basis of F2 hybrid breakdown.

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