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Direct evidence of recombination in human mitochondrial DNA

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Over the last 5 years, there has been considerable debate as to whether there is recombination in human mitochondrial DNA (mtDNA) (for references, see Piganeau and Eyre-Walker, 2004). That debate appears to have finally come to an end with the publication of some direct evidence of recombination. Schwartz and Vissing (2002), 2 years ago, presented the case of a 28-year-old man who had both maternal and paternally derived mtDNA in his muscle tissue – in all his other tissues he had only maternally derived mtDNA. It was the first time that paternal leakage and, consequently, heteroplasmy was observed in human mtDNA. In a recent paper, Kraytsberg *et al* (2004) take this observation one step further, and claim to show that there has been recombination between the maternal and paternal mtDNA in this individual.

There is a major possibility, in experiments of this nature, that the recombinants have been produced in laboratory, either by PCR, or by some other mistake. However, the authors have gone to great lengths to ensure that the recombinants are genuine, including repeating the experiment with a mix of maternal and paternal mtDNAs. They did not observe any recombination in this latter experiment, so we can be very confident that recombinants that they detected in the muscle tissue are genuine.

The direct demonstration of recombination in human mtDNA has a number of important implications. First, the results show that recombination between maternal and paternal mtDNA is possible. It has been known for sometime that paternal mtDNA enters the egg in humans (see Cummins, 2000), and that mammalian mitochondria contain the enzymes necessary to promote homologous recombination (Thyagarajan *et al*, 1996). However, there are efficient mechanisms that target paternal mtDNA for destruction once it is in the egg (Sutovsky *et al*, 2000), and there is no evidence that different mtDNAs would ever have the chance to recombine. If different mtDNAs are introduced into the same cell in different mitochondria, can be maintained in that state for many generations, without ever appearing in the same mitochondria (Enriquez *et al*, 2000).

Second, the results suggest that human mitochondria have an active recombination pathway. Human mtDNA has a high rate of evolution and this has been attributed to a lack of repair enzymes (Brown, 2001). The possibility of a recombination pathway suggested by these current results may also provide a further reason.

Human mitochondrial DNA has been used extensively to study the evolution of our species. However, most of the conclusions from these studies are likely to remain unaffected, either because they do not rely on the assumption of clonality, or because the level of recombination is such that its effects will be small. For example, mtDNA has been used to study the spread of humans across the globe (Cann, 2001). The genetic differences were probably established as human populations spread to new localities and have persisted because of reduced gene flow between distant populations. If there is little gene flow, there will be little opportunity for recombination. The one area in which recombination may have implications is dating events in human evolution. This is for two reasons – first, the phylogenetic tree may not represent the particular evolutionary events of interest; for example, a mtDNA tree may not represent the phylogeny solely of females if there is paternal leakage and/or recombination; it could not, therefore, be used to estimate the date of our most recent female common ancestor. Second, recombination will tend to generate homoplasies and therefore variation in the rate of nucleotide substitution between sites. This in turn will lead to an overestimate of the rate of nucleotide substitution if clonal inheritance is wrongly assumed.

Although Kraytsberg *et al* (2004) show very clear evidence of crossing-over in human mtDNA, there is little or no population genetic evidence of recombination. How can this be? There are two possibilities. One possibility is that, although Kraytsberg *et al* (2004) have detected recombination in a somatic tissue, it never occurs in the germ line. This seems unlikely, however. Alternatively, the explanation may be that recombination is difficult to detect in population genetic data, even if it is occurring at appreciable frequencies. This is because all methods for detecting recombination have low statistical power.

The results of Kraytsberg *et al* (2004) show that recombination has been fairly frequent in the individual they study. Even if we assume that all identical sequences are the product of the same recombination event, there must still have been 16 events. Unfortunately, this observation does not give us a handle on how frequent recombination is likely to be in the population, since this depends on the rate of paternal leakage; yet, we have no precise estimate of this parameter. At most, one presumes it must be less than 1 in 1000, since there are 100 000 mitochondria in the human egg and only 100 in the sperm (Satoh and Kuroiwa, 1991).

The challenge for the future will be to determine how frequent paternal leakage and recombination are in humans, and how frequent these processes are in other species.

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Brown TA (2001). Gene Cloning and DNA Analysis: an Introduction. Blackwell Sci: Oxford.
Cann RL (2001). *Science* **291**: 1742–1748.
Cummins JM (2000). *Hum Reprod* **15**(Suppl 2): 92–101.
Enriquez JA, Cabezas-Herrera J, Bayona-Bafaluy MP, Attardi G (2000). *J Biol Chem* **275**: 11207–11215.
Kraytsberg Y, Schwartz M, Brown TA, Ebralidse K, Kunz WS, Clayton DA *et al* (2004). *Science* **304**: 981.
Piganeau G, Eyre-Walker A (2004). *Heredity* **92**: 282–288.
Satoh M, Kuroiwa T (1991). *Exp Cell Res* **196**: 137–140.
Schwartz M, Vissing J (2002). *N Engl J Med* **347**: 576–580.
Sutovsky P, Moreno RD, Ramalho-Santos J, Dominko T, Simerly C, Schatten G *et al* (2000). *Biol Reprod* **63**: 582–590.
Thyagarajan B, Padua RA, Campbell C (1996). *J Biol Chem* **271**: 27536–27543.