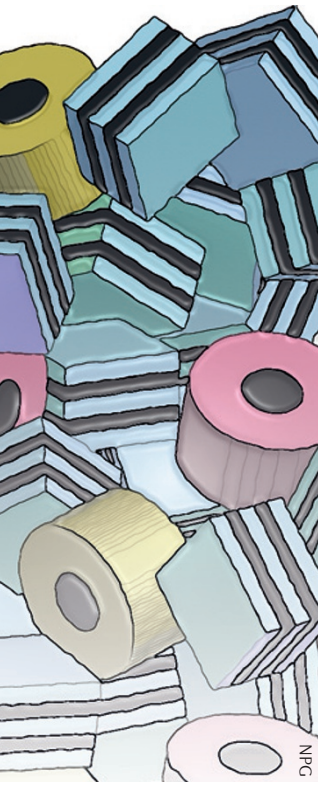
Nature Reviews Genetics | AOP, published online 8 May 2014; doi:10.1038/nrg3736



RNA

All sorts of mitochondrial RNA

High-resolution RNA sequencing of the mitochondrial genome has revealed a substantial level of sequence variation both within and between individuals, which has potential implications for human health. A new study now reports that mitochondrial RNA heterogeneity (that is, heteroplasmy) often occurs at the same functionally relevant position within tRNA genes and that the proportion of heteroplasmy within individuals is associated with a single variant in the nuclear genome. "We identified a remarkable amount of RNA sequence variation within each individual, which represents variation across mitochondrial transcriptomes," says Alan Hodgkinson (University of Montreal), co-first author of the study.

The researchers carried out high-throughput deep sequencing (>6,000×) of whole-blood RNA in a population sample of 708 individuals from the CARTaGENE project, led by Philip Awadalla (University of Montreal). An average of 14 heteroplasmic sites were recorded per individual, totalling 650 unique sites across all individuals. Thirteen of these sites were found to contain three or more nucleotides (that is, they were multiallelic) across most of the individuals sampled. The majority of these multiallelic sites are situated at the ninth position of tRNAs, and approximately half are known to be post-transcriptionally methlyated. Sequencing of the corresponding nuclear DNA revealed no variation, which indicates that these sites are candidates for RNA modification events.

Genome-wide analysis of nuclear DNA identified a missense mutation (rs11156878) in the mitochondrial RNase P subunit 3 (*MRPP3*; also known as *KIAA0391*) gene — which is involved in processing mitochondrial RNA — that has the strongest association with the intra-individual proportion of alternative counts and that accounts for 22% of the variance.

Analysis of the 1000 Genomes data showed that the minor allele frequency of rs11156878 is variable across individuals from different continents, which led the researchers to propose that this variant might have implications for region-specific health. "We find some evidence that the inferred level of post-transcriptional methylation is associated with basal metabolic rate, and it will certainly be interesting to consider whether the level of methylation is more extreme in certain disease contexts," concludes Hodgkinson.

Bryony Jones

ORIGINAL RESEARCH PAPER Hodgkinson, A. *et al.* High-resolution genomic analysis of human mitochondrial RNA sequence variation. *Science* **344**, 413–415 (2014)