

Large reservoir of mitochondrial DNA mutations identified in humans

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Researchers at the University of Newcastle, England, and the Virginia Bioinformatics Institute at Virginia Tech in the United States have revealed a large reservoir of mitochondrial DNA mutations present in the general population. Clinical analysis of blood samples from almost 3,000 infants born in north Cumbria, England, showed that at least 1 in 200 individuals in the general public harbor mitochondrial DNA mutations that may lead to disease.

The findings, which highlight the need to develop new approaches to prevent the transmission of mitochondrial diseases, were published in *The American Journal of Human Genetics*.

Mitochondria, the "engines" present in each cell that produce adenosine triphosphate, are passed from mother to offspring. Mutations in mitochondrial DNA inherited from the mother may cause mitochondrial diseases that include muscle weakness, diabetes, stroke, heart failure, or epilepsy. In almost all mitochondrial diseases caused by mutant mitochondrial DNA, the patient's cells will contain a mixture of mutant and normal mitochondrial DNA. The proportion of mutant mitochondrial DNA in most cases determines the severity of disease.

Previous estimates from epidemiological studies suggested that mitochondrial diseases affect as many as one person in 5,000. However, the incidence of new mitochondrial mutations and the prevalence of those carrying these mutations were never fully established due to limitations in the methods used. Most of the earlier estimates of the



frequency of mitochondrial DNA mutations in the general population, for example, have depended on identification of clinically affected patients and subsequent retracing of inheritance on the maternal side of the family. This approach fails to detect the gradual accumulation of mutations in some members of the population, including those individuals who harbor mitochondrial DNA mutations but who otherwise do not show the symptoms of disease.

Dr. David Samuels, Assistant Professor at the Virginia Bioinformatics Institute and an author on this study, commented: "We know from many clinical studies of patients and their families that our cells can tolerate a rather large amount of mutant mitochondrial DNA with no significant loss of function. From that observation we have suspected that there may be a large number of people in the general population who carry pathogenic mitochondrial DNA mutations, but who are not obviously ill with a mitochondrial disease. This study gives us, for the first time, a measurement of the number of these carriers of pathogenic mitochondrial DNA mutations in the general population. One in every 200 individuals is a lot of people – around 1.5 million people in the United States alone. "

The scientists looked at 10 mitochondrial DNA mutations (arising from single nucleotide replacements) often found in patients with mitochondrial disease. By taking advantage of a high-throughput genotyping system that uses mass spectrometry measurements, the researchers were able to detect mutated mitochondrial DNA at high sensitivity. In each positive case, DNA cloning and sequencing were used to confirm the findings. By looking at differences in tissue samples from mother and child, the researchers were also able to estimate the rate at which new DNA mutations had arisen in the population. The incidence of new mutations was close to 100 for every 100, 000 live births.



Dr. Samuels commented: "These new clinical measurements have given direct evidence for the widespread incidence of pathogenic mitochondrial DNA mutations in the human population. These findings emphasize the pressing need to develop effective ways to interrupt the transmission of these mutations to the next generation."

Citation: Hannah R. Elliott, David C. Samuels, James A. Eden, Caroline L. Relton, Patrick F. Chinnery (2008) Pathogenic mitochondrial DNA mutations are common in the general population. American Journal of Human Genetics 83(2): 254-260. doi:10.1016/j.ajhg.2008.07.004

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