Healthy people carry disease-causing mitochondrial DNA mutations

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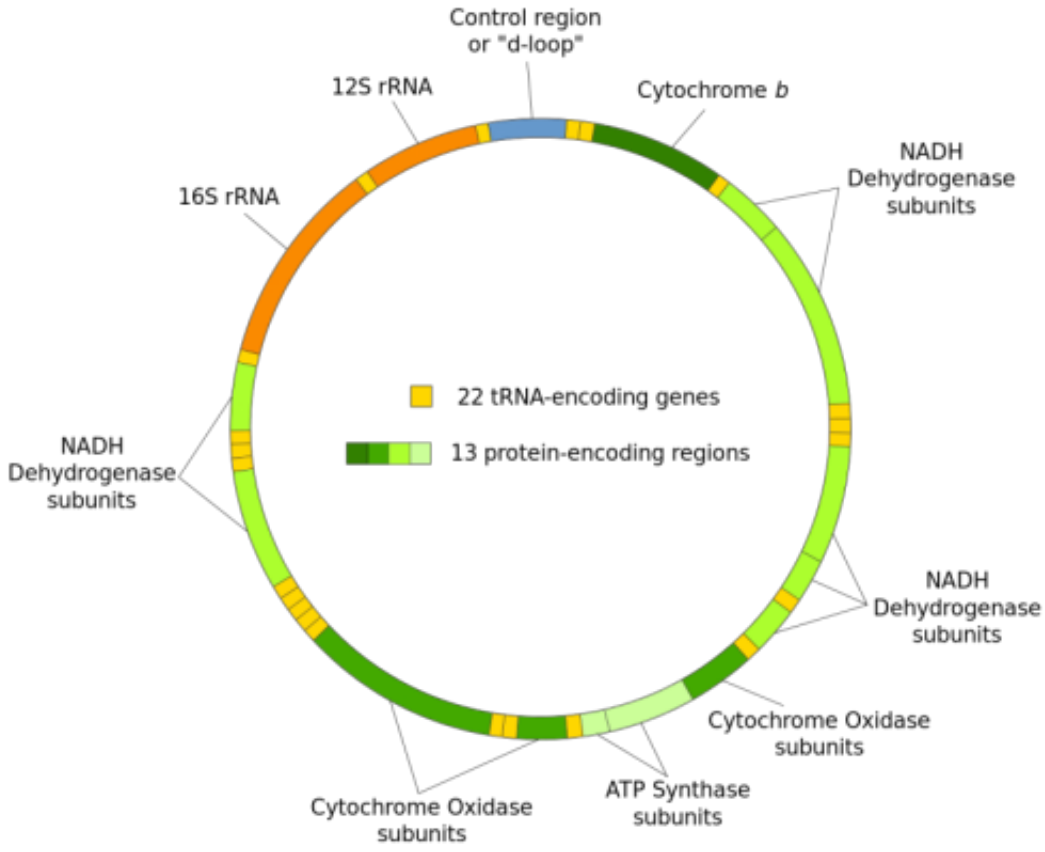

Structure of the human mitochondrial genome. Credit: Wikipedia/CC BY-SA 3.0

(Medical Xpress)—For the first time, researchers have discovered that disease-causing mutations in mitochondrial DNA (mtDNA) are common in healthy individuals, according to a Cornell study published July 7 in

the *Proceedings of the National Academy of Sciences*.

Previous studies have found associations between mtDNA mutations and many disorders, including cancers, diabetes, autonomous immune diseases, Parkinson's and other age-related diseases. The presence of disease-causing mtDNA mutations in healthy humans could play a major role in the aging process and age-related diseases, according to the study's authors. Future work will try to determine the extent that these mutations contribute to age-related disease.

Most human cells carry two copies of nuclear DNA, one copy from each parent, and hundreds of copies of mtDNA, inherited only from the mother.

The pathogenic mtDNA mutations in healthy individuals are usually present at low frequency within cells, but by random chance during cellular division, the number of pathogenic mutations within some cells can increase. "As individuals age, we expect the frequency of deleterious mutations to increase in a fraction of cells causing malfunctioning mitochondria and defective cells," said Zhenglong Gu, associate professor of nutritional sciences and the paper's senior author.

"If more than 60 percent of mtDNA carry pathogenic mutations, then there will likely be a problem for that cell," which could be a mechanism that contributes to the aging process and disease, said Kaixiong Ye, a graduate student in Gu's lab who is the paper's lead author.

These mutations are present because natural selection has not been strong enough to remove them, said the researchers. Natural selection would have removed deleterious mutations if they had caused disease that weakened individuals. However, pathogenic mtDNA mutations are usually present at low frequency and buffered by healthy mtDNA, preventing the action of natural selection.

The discovery is "not surprising in hindsight, but this is the first time using such a large dataset to unravel the prevalence of pathogenic mtDNA mutations in healthy individuals," said Ye.

The data in this study are from the 1000 Genomes Project, which has sequenced more than 1,000 human genomes but left mtDNA data unanalyzed. Gu hopes this study can raise interest in understanding the role of mtDNA in diseases.

In the next phases of this work, the researchers will investigate whether a healthy diet and lifestyle can slow down the expansion of pathogenic mtDNA mutations. They will also explore the effects of these mutations at the single cell level, investigate the percentage of cells with high-frequency defective mtDNA and determine what happens to these cells as a person ages: Do the cells die, and if they don't die, then what, Gu said.

More information: "Extensive pathogenicity of mitochondrial heteroplasmy in healthy human individuals," by Kaixiong Ye, Jian Lu, Fei Ma, Alon Keinan, and Zhenglong Gu.
www.pnas.org/cgi/doi/10.1073/pnas.1403521111

Provided by Cornell University