New findings show mitochondrial DNA fragments in blood as important biomarkers for aging and inflammation

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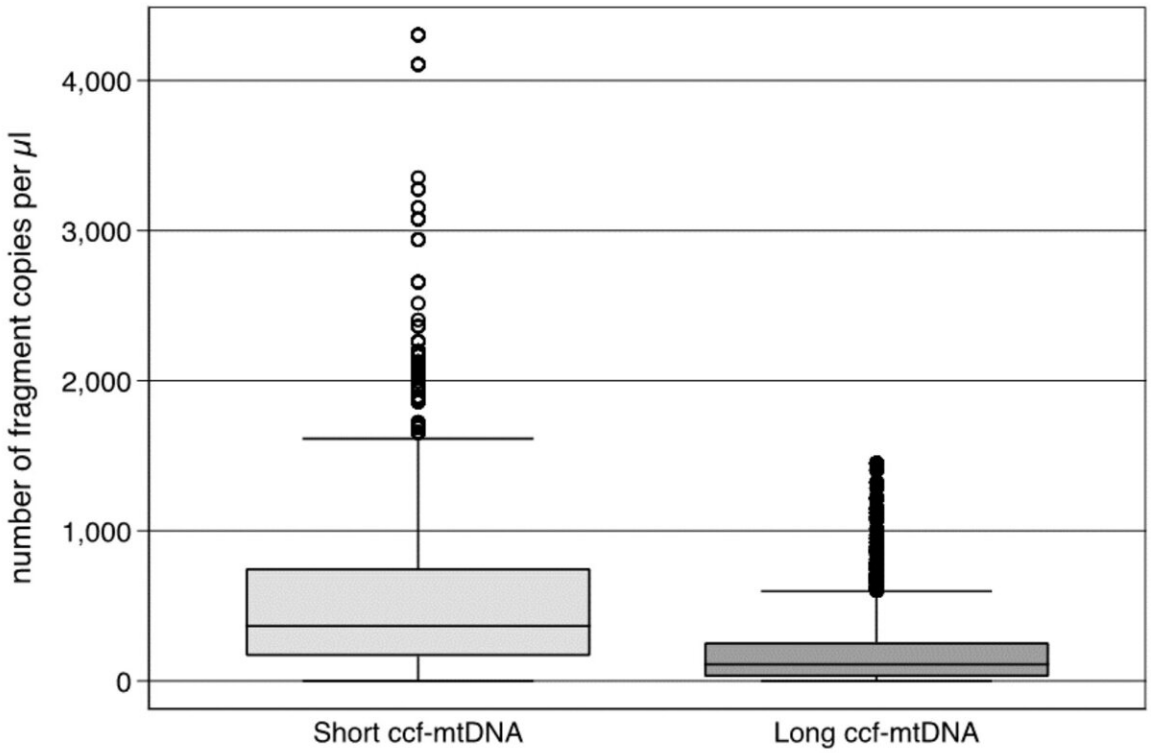

Boxplots of distributions for the ccf-mtDNA values (number of fragment copies per µl). Credit: *Immunity & Ageing* (2023). DOI: 10.1186/s12979-023-00342-y

In an eight-year study of more than 600 community-dwelling older

adults, Johns Hopkins Medicine researchers say they have further linked levels of cell-free DNA (DNA fragments resulting from cell death) circulating in the blood to chronic inflammation and frailty.

The study is novel and expands on previous work, the investigators say, because it focused on mitochondrial DNA rather than solely genomic DNA, as previously reported in October 2022.

The new findings, published in *Immunity & Ageing*, add to evidence that relatively high levels of DNA fragments found in routine blood samples could be accurate and useful biomarkers, or signals, for a wide range of cognitive and physical decline.

Analysis also found correlations between such DNA fragments and the presence of other well-known biomarkers for aging, including cytokine proteins, tumor necrosis factors (proteins made by the immune system in response to tumor growth) and proteins made by the liver when inflammation is present.

"By expanding the types of DNA screened for in the blood, the new research has expanded efforts to better understand and predict physical and cognitive declines that come with aging," says Peter Abadir, M.D., associate professor of geriatric medicine and gerontology at the Johns Hopkins University School of Medicine.

Previous studies by Abadir and Lolita Nidadavolu, M.D., Ph.D., assistant professor of geriatric medicine and gerontology at the Johns Hopkins University School of Medicine, focused solely on circulating cell-free genomic DNA (ccf-gDNA) as a possible biomarker for aging's cognitive and physical decline. The new work focused on mitochondrial DNA (ccf-mtDNA)—maternally inherited DNA found in cellular organelles and often described as "power plants" in the cells of humans, other animals, plants and most other organisms

When cells die via natural programmed cell death (apoptosis), mitochondrial DNA is broken into small fragments and left to circulate in the blood, much the same as genomic DNA. If a catastrophic event such as injury, blood flow interruptions or disease causes cell death, larger mitochondrial DNA fragments will be found that can trigger chronic inflammation—an immune response that mimics what happens when the body reacts to bacteria and viruses.

Chronic inflammation has been shown over time to result in symptoms of frailty and memory loss and other cognitive decline.

For the new study, researchers analyzed blood samples drawn in the mid-1990s from 672 community-dwelling men and women with an average age of 80 at the beginning of the study period. The participants were pulled from three cohort studies based at the RUSH Alzheimer's Disease Center. The study groups are the Religious Orders Study, the Memory and Aging Project and the Minority Aging Research Study.

All participants received yearly physical and cognitive testing at the time of each blood draw. Cognitive tests included memory, perception and physical tests of grip strength, gait, fatigue and motor function. Researchers then compared levels of long and short CCF-mtDNA fragments against four known biomarkers of inflammation: cytokine proteins, two tumor necrosis factors and inflammatory liver proteins.

Results showed close relationships between the four biomarkers and increased amounts of CCF-mtDNA. For example, if a patient's blood sample had high amounts of one or more of these known biomarkers for inflammation, the sample also contained high amounts of CCF-mtDNA. Also, researchers found that while high amounts of genomic circulating DNA were linked to cognitive and physical decline, high levels of mitochondrial DNA were more strongly linked to physical decline only.

"Our goal is to promote healthy aging, which means prolonging 'health span,' preserving quality of life and maintaining energy for older adults," says Nidadavolu. "The more we can learn about why some patients take the path to frailty or dementia and others don't, the more interventions we can identify and recommend to preserve health as people age. Identifying circulating DNA in the blood as a biomarker is just the beginning of this research."

The researchers say their next steps include expanding study populations to younger adults to identify the earliest time these cell-free DNA fragments become prevalent in blood samples. Additionally, they hope to determine exactly how these DNA fragments contribute to inflammation and how to possibly intervene before they become a precursor to cognitive and physical decline.

More information: Lolita S. Nidadavolu et al, Associations between circulating cell-free mitochondrial DNA, inflammatory markers, and cognitive and physical outcomes in community dwelling older adults, *Immunity & Ageing* (2023). DOI: 10.1186/s12979-023-00342-y

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