Nature Reviews Neurology **9**, 601 (2013); published online 1 October 2013; doi:10.1038/nrneurol.2013.207

ALZHEIMER DISEASE

Variations in mitochondrial DNA predict AD-related brain atrophy

Skypixel | Dreamstime.com

Mitochondrial DNA (mtDNA) polymorphisms are associated with key neuroimaging characteristics of Alzheimer disease (AD), report researchers at the University of Kansas Alzheimer's Disease Center. Robyn Honea's team found that some mitochondrial haplogroups were associated with global and regional brain atrophy, which is a marker for AD risk and progression.

Honea and colleagues had previously investigated the contribution of family history to risk of AD. According to Honea, atrophic brain changes that indicate a high risk of AD are often found in individuals with a maternal family history of AD, even when they are healthy. On the basis of this maternal inheritance pattern and the mtDNA mutation findings, Honea and other researchers hypothesized that changes in mtDNA might confer an increased risk of AD. "Dysfunctioning mitochondria are known to be a part of Alzheimer's disease, and it is the mother that contributes mitochondrial DNA to her offspring," summarizes Honea.

The researchers assigned 645 patients (154 with AD, 316 with mild cognitive impairment, and 175 controls) to mitochondrial haplogroups on the basis of 138 small nucleotide polymorphisms in their mtDNA. They combined this haplogroup information with volumetric MRI data, available publically through the Alzheimer's Disease Neuroimaging Initiative. The database included at least two brain scans from each individual, enabling the researchers to assess changes in hippocampal atrophy over 2 years.

Previous studies have used a clinical diagnosis of AD to test whether mutations in mtDNA are associated with the disease, but Honea and her team might be the first to link mtDNA variations with brain imaging markers of AD. "Since a diagnosis of AD is only made after symptoms have already manifested, sometimes years into the disease, we decided to use brain imaging biomarkers, as a possibly more sensitive marker of the disease process," explains Honea.

The group found that individuals who belonged to certain haplogroups were more likely to have diminished whole brain volume, as well as atrophy in the hippocampal formation and rostral temporal lobe—all known neuroimaging markers for AD. Their findings are in line with those of previous studies, which linked mitochondrial haplogroups U and K to an increased risk of AD.

The team plans to extend their studies into larger populations and other biomarkers, and is developing approaches to treat brain ageing by targeting mitochondrial dysfunction.

Hemi Malkki

Original article Ridge, P. G. *et al.* Mitochondrial haplotypes associated with biomarkers for Alzheimer's disease. *PLoS ONE* **8**, e74158 (2013)