How misplaced DNA could influence disease risk

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Credit: AI-generated image (disclaimer)

DNA is our body's instruction manual. It contains all the information that our cells need to make proteins and other molecules vital for our development, growth and survival.

We inherit two different types of DNA from our parents: nuclear and

mitochondrial DNA (mtDNA). Nuclear DNA is an equal mixture from both parents. mtDNA we only inherit from our mothers. It encodes essential components needed by our mitochondria to produce energy.

Mitochondria are the powerhouses or batteries of our cells. Consequently, genetic changes (or variants) in the mtDNA sequence can affect the energy production in our cells.

Genetic variants happen naturally. Most are harmless. When these variants are harmful, they can reduce the amount of energy produced in our cells. The loss of energy may cause cells that are especially dependent on energy (such as our brain cells or heart cells) to not function very well or even die. This in turn, could lead to the onset of diseases such as Alzheimer's and Parkinson's.

Parkinson's disease is an incurable disease affecting nerve cells in the brain. These cells require lots of energy. They normally produce a chemical called dopamine which helps to regulate our movements and emotional responses. In individuals with Parkinson's disease these nerve cells die and not enough dopamine is produced in the brain. As a result, people with Parkinson's experience symptoms which affect their physical movements (resting tremors, loss of balance) as well as their mood and emotions (depression).

Our understanding of Parkinson's disease is far from complete, especially in diverse societies such as South Africa. But researchers now believe that in most cases, Parkinson's is caused by a complex interaction between genetic (genetic variants) and environmental factors (for example exposure to environmental toxins). These factors likely interfere with the healthy functioning of dopamine-producing neurons in the brain.

Identifying potential genetic variants that influence Parkinson's risk is

key to understanding the disease better. It could also help develop better, more targeted treatments that are effective in local populations as well as the well-studied European or Asian populations.

Our research group aims to uncover the genetic factors contributing to Parkinson's disease in South Africa's diverse local population. Previous research has found that genetic risk factors likely differ among populations.

Human evolution

Throughout human evolution, genetic variants have been passed on from one generation to the next, together with new ones from each generation. This has allowed our mtDNA to accumulate lots of genetic variants. The accumulation of such genetic variants in maternal lineages has led to the formation of so-called haplogroups (denoted by letters) or maternal genetic ancestry. People belonging to the same haplogroup share a common set of mtDNA variants.

Recent evidence from studying Leber's Hereditary Optic Neuropathy (LHON), an mtDNA-affecting disease that results in vision loss, suggests that common, otherwise harmless, mtDNA variants could be harmful if they occur "out-of-place" on an uncommon haplogroup background.

In a recent study, my colleagues and I hypothesized that mitochondrial dysfunction, resulting from the "incompatibility" of common haplogroup variants, could also play a role in predisposing people to more common and complex diseases such as Parkinson's.

African ancestry

Common mtDNA variants that occur "out-of-place" have previously

been shown to cause mitochondrial dysfunction. And mitochondrial dysfunction has repeatedly been implicated in Parkinson's disease. Based on this knowledge our research group set out to investigate whether such "out-of-place" variants could contribute to Parkinsons's risk in our local African population.

Our study is the first to investigate mtDNA in African ancestry individuals living with Parkinson's disease. It's also the first to explore the role of "out-of-place" mtDNA variants in Parkinson's risk.

To investigate this, we sequenced the whole mtDNA of individuals with Parkinson's and healthy volunteers without Parkinson's.

In total we had two groups of people with Parkinson's disease. One group of African ancestry cases and another group of European ancestry cases. We additionally had three groups of healthy volunteers: two of African ancestry and one of European ancestry.

The findings

We found significantly more African ancestry people with Parkinson's carrying "out-of-place" variants compared to the healthy volunteers from one of the two African control groups.

But we didn't see this significant difference when comparing the African Parkinson's cases to the second African control group. We also didn't pick up this difference when we compared the European ancestry Parkinson's disease cases to the European volunteers.

The mixed results mean that we can't say for sure that "out-of-place" variation could be a genetic risk factor for Parkinson's in the local African ancestry population, but not in the European population. More studies that replicate our findings would be needed to confirm this.

Consequences

Although we could not replicate our findings across all of our study groups, our one significant finding extends the possible role of "out-of-place" variants in disease, from mtDNA-related mitochondrial disease to Parkinson's.

We speculate that "out-of-place" variants could cause subtle changes in the cell's energy production. This, together with additional Parkinson's risk factors (for example genetic variants in nuclear DNA or exposure to environmental toxins), could contribute to mitochondrial dysfunction that ultimately leads to disease onset.

These "out-of-place" variants are considered common and thought to be less harmful than rare ones. However, our work together with that of others, highlights the importance of considering "out-of-place" mtDNA variants in disease as these variants may have the potential to inflict harm when taken out of context.

To effectively treat and eventually cure complex diseases such Parkinson's, we first need to identify all their causes. Additional studies confirming "out-of-place" variation as another potential genetic contributor to disease, bring us one step closer to piecing together the complex puzzle that is Parkinson's.

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