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Cell powerhouse sequencing technology provides deeper look at inherited disease risk

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A new sequencing technique may provide a clearer picture of how genes in mitochondria, the "powerhouses" that turn sugar into energy in human cells, shape each person's inherited risk for diabetes, heart disease and cancer, according to a study conducted at the Icahn School of Medicine at Mount Sinai and published online this week in the journal *Nucleic Acids Research*.

The powerful new tool may help researchers better explain why some people get sick and others do not despite being the same age and weight, or having the same bad habits (e.g. smoking). Researchers have long sought to determine these risks by looking at diet and variations in nuclear genes inherited from both parents. These analyses have left out differences in mitochondrial genes (mtDNA), the second kind of DNA in every cell, which we inherit from our mothers.

Research in recent years revealed that miscues in mitochondrial energy production can cause several diseases. Determining the contribution of variations in mtDNA to a person's disease risk is complicated by heteroplasmy, where DNA in different sets of mitochondria across many cells, randomly change over time, resulting in slightly different DNA code, and so a differing genetic component of risk.

The Mount Sinai study developed the sequencing technology, called Mseek, which helped accurately identify heteroplasmy in a person's mtDNA for the first time. Past efforts in this regard had been hindered by the very small amounts mtDNA in each cell. Studies had documented

heteroplasmy, but none had established it conclusively at the single cell level.

"Researchers have struggled to sequence mtDNA accurately and in a cost effective manner," said Ravi Sachidanandam, PhD, Assistant Professor, Oncological Sciences, Icahn School of Medicine at Mount Sinai. "The technique we have developed will allow us to identify dysfunction within mitochondria and makes mtDNA a useful biomarker as well as a potential therapeutic target in cancer and many inherited diseases."

Dr. Sachidanandam said the new technology shows unprecedented sensitivity, specificity and sequencing depths. It also has the ability to yield highly pure mtDNA and to detect different versions of mtDNA code or variants.

The Mseek technique uses enzymes to purify mitochondrial DNA by deleting the nuclear DNA, leaving behind the pure mitochondrial DNA to be sequenced. By applying Mseek to several cell lines, researchers identified mtDNA "fingerprints" in each cell sample. Additionally, they established that heteroplasmy is stably maintained at a single-cell level over multiple divisions by tracking mtDNA variants.

"We hypothesized that heteroplasmy could be stabilized by intercellular exchange of mtDNA," said Sachidanandam. "Our results demonstrated the exchange of mtDNA is possible and heteroplasmy can be maintained stably through this mechanism. This technique could provide a novel platform to investigate features of heteroplasmy in normal and diseased state and in the future, the exchange mechanism could be used as a treatment that targets bad mtDNA and exchanges it with good mtDNA."

Provided by The Mount Sinai Hospital