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Steadily rising increases in mitochondrial DNA mutations cause abrupt shifts in disease

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New work by a pioneering scientist details how subtle changes in mitochondrial function may cause a broad range of common metabolic and degenerative diseases. Mitochondria are tiny energy-producing structures within our cells that contain their own DNA.

The new research shows that small changes in the ratio of mutant to normal mitochondrial DNA within the thousands of mitochondrial DNAs inside each cell can cause abrupt changes in the expression of numerous genes within the nuclear DNA. Furthermore, the different proportions of mutant mitochondrial DNA that result in altered nuclear gene expression correspond to the same proportions of mutations in mitochondrial DNA that are associated with diabetes and autism; brain, heart and muscle disease; or lethal infantile disease.

"By showing that subtle changes in the cellular proportion of the same mitochondrial DNA mutation can result in a wide range of different clinical manifestations, these findings challenge the traditional model that a single mutation causes a single disease," said study leader Douglas C. Wallace, Ph.D., director of the Center for Mitochondrial and Epigenomic Medicine at The Children's Hospital of Philadelphia. He added, "The research offers key insights into understanding the underlying cause of metabolic and neurodegenerative disorders such as diabetes, Alzheimer, Parkinson and Huntington disease, as well as human aging."

"The discrete changes in nuclear gene expression in response to small increases in mitochondrial DNA mutant level are analogous to the phase changes that result from adding heat to ice," said Wallace. "As heat is added, the ice abruptly turns to water and with more heat, the water turns abruptly to steam." Here a quantitative change (an increasing proportion of mitochondrial DNA mutation) results in a qualitative change (coordinate changes in nuclear gene expression together with discrete changes in clinical symptoms).

The study by Wallace and colleagues appeared online Sept. 3 in the *Proceedings of the National Academy of Sciences*.

Existing in hundreds or thousands of copies outside the nucleus of every cell, mitochondria have their own DNA, distinct from the well-known DNA inside the cell nucleus. Although mitochondrial DNA (mtDNA) holds far fewer genes than nuclear DNA, mtDNA exchanges signals with nuclear DNA and participates in complicated networks of biochemical reactions essential to life.

Wallace's current study rests on his investigations into the mysteries of mitochondria for over 40 years. In 1988, he was the first to demonstrate that mitochondrial DNA mutations can cause human disease. He has

continued to build a body of research into mechanisms by which mutations in mtDNA contribute to both rare and common diseases by disrupting the body's energy production.

In the current study, Wallace's team investigated the impacts of steadily increasing levels of a pathogenic mutation in one particular base of mitochondrial DNA.

Researchers already knew that if 10 to 30 percent of a person's mitochondrial DNA has this mutation, a person has diabetes, and sometimes autism. Individuals with an mtDNA mutation level of 50 to 90 percent have other multisystem diseases, particularly MELAS syndrome, a severe condition which involves brain and muscle impairments. Above the 90 percent level, patients die in infancy.

In the current study, conducted in cultured human cells, Wallace and colleagues analyzed cells with different levels of this pathogenic mtDNA mutation to determine the effects on the gene expression of the cell. The researchers measured variations in cellular structure and function, nuclear gene expression, and production of different proteins.

"The mutations in mitochondria impair their ability to produce energy, and mitochondria transmit distress signals to the cell nucleus," said Wallace. "But the nucleus can respond in only a limited number of ways." Those responses may manifest themselves in discrete, profound consequences for patients.

Findings May Extend to Common Conditions

Wallace argues that the medical significance of this research extends beyond the province of the relatively rare disorders typically classified as mitochondrial diseases. The gene expression profile—the pattern of gene activity seen at the level at which mtDNA mutations trigger brain

disorders—parallels the profiles found in Alzheimer, Parkinson and Huntington diseases. "The findings in this study provide strong support for the concept that common metabolic diseases such as diabetes and obesity, heart and muscle diseases, and neurodegenerative diseases have underpinnings in energy deficiencies from malfunctioning mitochondria," said Wallace. "Thus this concept brings together a cluster of diseases previously considered to be separate from one another."

Significantly, Wallace added that the research also pertains to aging. Because mitochondrial mutations accumulate as people age, mitochondrial energy production declines, with deleterious effects on the heart, the brain and on interrelated biological systems that sustain health and life.

Next steps in research, says Wallace, include investigations of how different diseases are associated with the sorts of abrupt phase changes his group found in the current cellular study. Some of the cellular changes, signaling patterns and protein activity levels found in the current research might become useful biomarkers in disease studies and drug development. "For instance, a preclinical screen for potential drugs that could reverse gene expression profile changes of the mitochondrial DNA mutant cells could reveal new therapies," he added.

Wallace's current study reinforces arguments he has presented over the course of his career, that mitochondria play a central, largely under-recognized role in all common human diseases. He has long argued that a traditional biomedical approach focusing on anatomy and individual organs does not provide the insights generated from a systems biology, bioenergetics-focused approach.

Wallace's paradigm-shifting hypotheses remain controversial in biomedicine. This latest study, he says, implies that the complexity of common diseases is rooted in the disconnect between continuous, linear

changes in mtDNA mutations and the discontinuous, sudden phase changes in nuclear gene expression that result. Even as his overall arguments about the role of mitochondria contend for broader acceptance, the current findings may provide useful, versatile tools for understanding and treating disease.

More information: "Progressive increase in in mtDNA 3243A>G heteroplasmy causes abrupt transcriptional reprogramming," *Proceedings of the National Academy of Sciences*, Early Edition published online Sept. 3, 2014. doi.org/10.1073/pnas.1414028111

Provided by Children's Hospital of Philadelphia

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