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In next-gen DNA sequence, new answers to a rare and devastating disease

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In Leigh syndrome, infants are born apparently healthy only to develop movement and breathing disorders that worsen over time, often leading to death by the age of 3. The problem is that the mitochondria responsible for powering their cells can't keep up with the demand for energy in their developing brains.

Now, researchers reporting in the September issue of Cell Metabolism, a Cell Press publication, have discovered a new genetic defect that can lead to the disease. The findings were made by sequencing a subset of about 1,000 genes encoding proteins active in the mitochondria in just two individuals with Leigh syndrome.

"This shows the huge potential of sequencing technologies to improve diagnosis," says David Thorburn of Murdoch Childrens Research Institute in Australia. "It's an all-comers approach that can be applied to individuals, even with no family history."

Leigh syndrome is the most common recognized mitochondrial disease of childhood, and the new genetic discovery adds to a growing list of about 40 genes known to cause Leigh syndrome when mutated.

The gene they uncovered encodes an enzyme active in mitochondria known as MTFMT (for mitochondrial methionyl-tRNA formyltransferase). (Mitochondria carry DNA of their own and their operation depends on a combination of proteins encoded locally and others encoded in the nuclear genome of a cell and imported.)

The MTFMT enzyme encoded in the mitochondrial DNA is responsible for converting a transfer RNA (tRNA) into a form used to initiate protein translation. Without that enzyme, mitochondria fail to translate proteins efficiently leading to the symptoms recognized as Leigh syndrome. Studies in patient skin cells showed that the defects in translation could be corrected by replacing the MTFMT gene.

Although it isn't clear in the case of Leigh syndrome whether a precise molecular diagnosis will necessarily lead to therapies, the current findings represent a meaningful advance.

"It can be very reassuring to families to have a definitive answer," Thorburn says. "They are often referred around from one doctor to another. A diagnosis at least provides some closure to the diagnostic odyssey even without a treatment."

Diagnosis of the disease along with its specific genetic cause can also be informative about the risk a couple has of having another affected child, he adds. The diagnostic information can help in decisions about whether and how to pursue alternative means of having children, for instance through the use of donor sperm or eggs.

In addition to their clinical implications, the new findings offer insight into the biology and evolution of human mitochondria. Mitochondria originated from bacteria that were engulfed by another cell, and their use of the modified tRNA to initiate translation is a relic of that microbial past.

"It's not clear why this requirement would have been maintained," Thorburn says. "It means that if mitochondrial proteins enter the circulation, say after a traumatic injury, they are mistaken for bacterial proteins, triggering a systemic inflammatory response."

Provided by Cell Press