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Collaboration rapidly connects fly gene discovery to human disease

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A collaborative study by scientists at Baylor College of Medicine (BCM) and the Montreal Neurological Institute of McGill University, and published March 20 in the online, open access journal *PLoS Biology*, has discovered that mutations in the same gene that encodes part of the vital machinery of the mitochondrion can cause neurodegenerative disorders in both fruit flies and humans.

Vafa Bayat in Dr. Hugo Bellen's lab at BCM, examined a series of mutant fruit flies for defects leading to progressive degeneration of photoreceptors in the eye. They identified mutations in the fruit fly gene that encodes a mitochondrial enzyme known as the mitochondrial methionyl-tRNA synthetase (Aats-met). These mutations also shortened life span and caused other problems, including reduced cell proliferation.

Mitochondria are the power plants of the cell, and have their own mechanism for producing proteins, separate from the main cellular protein-producing machinery. Defects in genes that encode mitochondrial proteins have been previously associated with human metabolic and neurological disorders.

Dr. Bayat, a recent graduate from the Program in Developmental Biology at BCM, searched the medical literature for genetic neurological disorders that were thought to be caused by defects in the region of our genome that contains the human version of the Aats-met gene, MARS2. One such disease, Autosomal Recessive Spastic Ataxia with frequent Leukoencephalopathy (ARSAL), had already been mapped to this region

of the genome by Dr. Bernard Brais and his colleagues, but the precise gene responsible was not known. Ataxias such as ARSAL are progressive neurodegenerative diseases that cause coordination problems, leading to modified gait and speech as well as other problems.

Dr. Isabelle Thiffault from the Montreal team identified complex rearrangements of the genetic material in the MARS2 gene of ARSAL patients. These unusual rearrangements resulted in reduced levels of the MARS2 enzyme, reduced synthesis of proteins by the mitochondria, and impaired mitochondrial function. As with the fruit fly mutants, the patients' cells also had increased levels of reactive oxygen species, which can damage cells and their genetic material, and slow cell proliferation.

"We found the same defect in the mitochondrial respiratory chains in the human cells, which produced a lot of reactive oxygen species," said Dr. Bayat. "When we feed the fly larvae antioxidants, they suppress the degenerative phenotypes in flies." The ability of antioxidants to counteract the negative consequences of the mutant gene in flies raises the possibility that a related approach might have beneficial effects in human patients, though this remains to be determined.

"While the discovery of mutations in fly genes has been linked to human disease before, it has often taken many years to decades to accomplish this," said Dr. Bellen. "This was a relatively quick process. In summary, we have shown that you can use flies to identify fly mutants with neurodegenerative phenotypes and that these mutants can assist in the identification of human disease genes."

More information: Bayat V, Thiffault I, Jaiswal M, Tétreault M, Donti T, et al. (2012) Mutations in the Mitochondrial Methionyl-tRNA Synthetase Cause a Neurodegenerative Phenotype in Flies and a Recessive Ataxia (ARSAL) in Humans. *PLoS Biol* 10(3): e1001288. doi:10.1371/journal.pbio.1001288