Devastating 'founder effect' genetic disorder raced to defective mitochondria in cerebellar neurons

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Defective mitochondria, the energy-producing powerhouses of the cell, trigger an inherited neurodegenerative disorder that first shows itself in toddlers just as they are beginning to walk, Canadian scientists reported at the American Society for Cell Biology Annual Meeting, Dec. 6, in Denver.

The disorder, Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS), was first identified in the late 1970s among the descendants of a small population of 17th century French immigrants who settled in the Charlevoix and the Saguenay River regions northeast of Quebec City.

At the ASCB meeting, a team of researchers at the Montreal Neurological Institute at McGill University and the Centre Hospitalier de l'Université Montréal (CHUM), reported that they had traced the cellular basis of ARSACS to disruptions in neuronal mitochondria, particularly in Purkinje cells in the cerebellum.

The identification of defective mitochondria as the cellular mechanism underlying ARSACS follows a series of discoveries that were made possible by the relatively high incidence (one in 1,500 to 2,000 in this Canadian population) of ARSACS and detailed genealogical records on this population.

In 2000, scientists pinpointed the genetic mutation responsible for the disease, and subsequently identified the massive 4,579 amino acid protein, named sacsin, coded by the ARSACS gene.

Over 100 separate mutations have been found in people diagnosed with ARSACS in Japan, Turkey, and across Western Europe.

The researchers, led by Peter McPherson, Ph.D., Paul Chapple, Ph.D., and Bernard Brais, M.D., Ph.D., developed a genetically modified mouse model that could not produce the normal sacsin protein.

The sacsin-knockout mice developed neurons with abnormally shaped and poorly functioning mitochondria, the organelles that act as energy-producing powerhouses in cells.

This disruption led to the eventual death of individual neurons within the Purkinje layer of the cerebellum. The same result occurred when the scientists repeated the experiment in a laboratory culture of neurons in which sacsin was knocked down by a lentiviral system driving inhibitory RNA.

McPherson said that at the cellular level, ARSACS is similar to such neurodegenerative diseases as Huntington's, Parkinson's, and Alzheimer's.

ARSACS has minimal effects on cognitive functions but instead concentrates its damage within the cerebellum, the center of muscle coordination at the base of the brain. The unsteadiness of gait, or ataxia, in children with ARSACS worsens, progressing through a growing list of difficulties with coordination, muscle wasting, uncontrolled eye movement, retinal streaks, peripheral neuropathy, and impaired speech. By the age of 40, most ARSACs patients must use wheelchairs.