Medical Xpress

New genetic disorder of balance and cognition discovered

December 7 2012

The family of disorders known as ataxia can impair speech, balance and coordination, and have varying levels of severity. Scientists from the Universities of Oxford and Edinburgh have identified a new member of this group of conditions which is connected to 'Lincoln ataxia', so called because it was first found in the relatives of US President Abraham Lincoln. The results are published in the journal *PLOS Genetics*.

Lincoln ataxia affects the cerebellum, a crucial part of the brain controlling movement and balance. It is caused by an alteration in the gene for 'beta-III spectrin', a protein found in the cerebellum. Each person has two copies of a gene, and in Lincoln ataxia there is an alteration in only one of the two copies. Unexpectedly, the British scientists have found cases of alterations in both copies of the gene, causing a novel disorder called 'SPARCA1' which is associated with a severe childhood ataxia and cognitive impairment.

This is the first report of any spectrin-related disorder where both copies of the gene are faulty and has given important insights into both Lincoln ataxia and SPARCA1.

The work was done using whole genome sequencing, a relatively new technology which allows all of a person's genetics information to be analysed. In addition to sequencing work, the scientists characterized the condition using mice lacking beta-III spectrin. This analysis, combined with previous work, links the protein defect to changes in nerve-cell shape in the brain areas associated with cognition and coordinated

movements. The work shows that loss of normal beta-III spectrin function underlies both SPARCA 1 and Lincoln ataxia, but a greater loss of beta-III spectrin is required before cognition problems arise.

The combination of methods used in this study highlight a broad role for spectrin in normal brain function beyond the cerebellum. There are many brain spectrins and the team are now searching for other abnormalities of spectrin function, as they believe these are part of an expanding group of conditions known as "neuronal spectrinopathies".

Provided by Public Library of Science