Genetic mutation causes ataxia in humans and dogs

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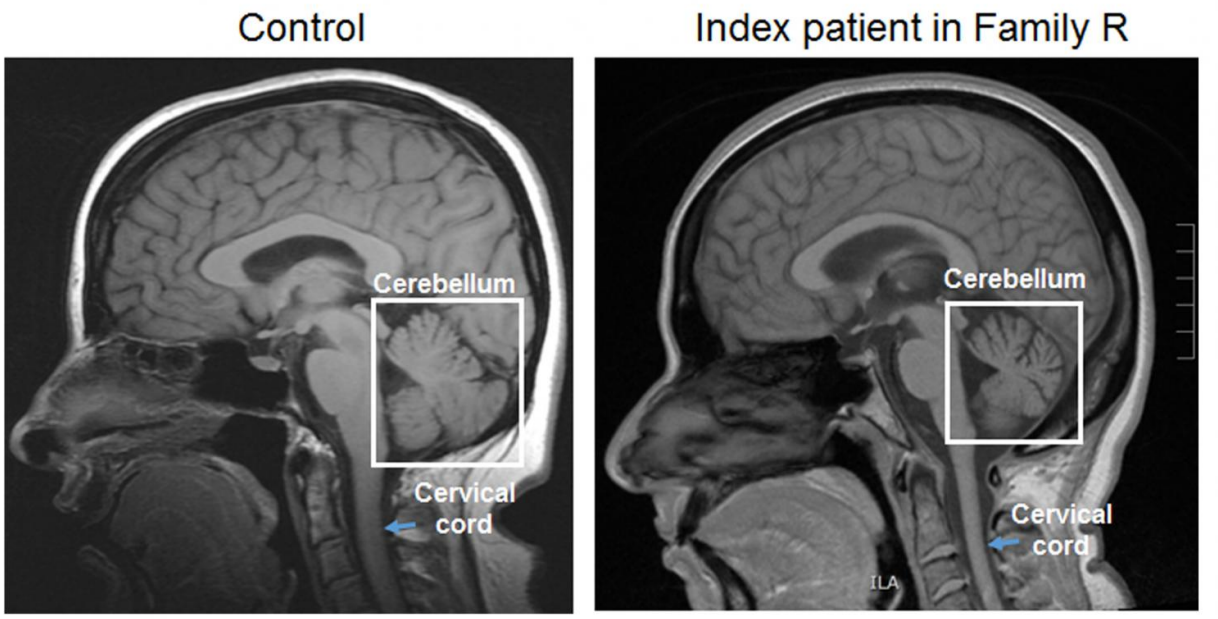

An MRI scan showing a healthy control (left) and a patient with cerebellar ataxia (right). The ataxia patient's MRI shows cerebellar atrophy and cervical spinal cord thinning. Repeat MRIs showed the atrophy slowly progressed over time. Credit: Wang et al./*Cell Reports* 2016

Cerebellar ataxia is a condition of the cerebellum that causes an inability to coordinate muscle movements. A study publishing June 16 in *Cell Reports* now describes a new genetic mutation as an additional cause of ataxia in humans and mice. The mutation, in the gene CAPN1, affects

the function of the enzyme calpain-1 and causes abnormal brain development. The same genetic mutation is also associated with ataxia in Parson Russell Terrier dogs.

"There are a number of genes linked to motor function that can be involved in ataxia when mutated," says Michel Baudry, a neurobiologist at Western University of Health Sciences. "Not only have we identified another, but we've also refined our understanding of the calpain enzymes, which is important because several companies have been talking about using calpain inhibitors to treat neurodegenerative diseases."

Calpain is an enzyme involved with learning, memory, and neurodegeneration in the brain, but it comes in two major forms—calpain-1 and calpain-2. "Nobody could make much progress on figuring out what each form of calpain was doing, because most of the pharmacological studies used molecules that inhibit both types at once" says Baudry. But about eight years ago, Baudry's team obtained a line of mice genetically engineered to lack only calpain-1 to examine the differences.

Baudry's mouse studies caught the attention of Henry Houlden, a neurologist at University College London, who was leading a team investigating ataxia. "Around two years ago, we identified two families with CAPN1 mutations with ataxia and spasticity," Houlden explains. Once the researchers determined that the mutation affected calpain-1's function, they looked up Baudry's work on the calpain-1 knockout mice. "Together, we started to investigate the function of this gene," says Houlden. The current study includes four families with members that have CAPN1 mutations and display symptoms of ataxia.

Baudry's team started testing whether the knockout mice had ataxia by tracking their balance when placed on a rotating rod. "We had never

looked at the cerebellum in our mice before," says Baudry. "But sure enough, we found that they had mild cerebellar ataxia."

The researchers demonstrated that during the first week after birth, the mice lacking calpain-1 had a much higher rate of neuronal death in their cerebellum, as compared to normal mice, and many of their synapses failed to mature.

"Calpain-1 is neuroprotective," explains Baudry. "When the brain matures, excess neurons are supposed to be pruned—but calpain-1 prevents that process from getting out of control." The team further determined that calpain-1 works normally by degrading an enzyme called PHLPP1, a protein phosphatase involved in programmed cell death. Injecting another compound involved in the pathway during the first postnatal week caused the newborn mice with CAPN1 mutations to develop normally.

Pharmacologically, the attempts to use calpain inhibitors in the clinic may not be working because they don't discriminate between calpain-1 and calpain-2, says Baudry: "If you want to try to address neurodegeneration, you have to use a calpain-2 inhibitor." Baudry is currently working with a team to develop calpain-2 inhibitors as neuroprotective drugs, under the umbrella of a new company called NeurAegis.

More information: *Cell Reports*, Wang et al.: "Defects in the CAPN1 gene result in alterations in cerebellar development and in cerebellar ataxia in mice and humans" www.cell.com/cell-reports/full … 2211-1247(16)30627-1 , DOI: 10.1016/j.celrep.2016.05.044

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