

Research Update

What's bred in the nerves: discovering the gene for a rare neurodegenerative disease

Researchers at McGill University and other institutions have found a genetic mutation that causes autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), a neurodegenerative disease that is one of many genetic disorders found in a demographically isolated part of northeastern Quebec (*Nat Genet* 2000;24:120-5). The gene involved is the largest uninterrupted length of protein-coding DNA sequence ever discovered in a vertebrate.

The researchers report cloning of the *SACS* gene on chromosome 13q11. The gene consists of a single, gigantic 12 794-bp exon, the scientists said.

ARSACS is an early-onset familial spastic ataxia characterized by prominent myelinated retinal nerve fibres, reduced motor-nerve velocity and absence of sensory-nerve conduction. Of more than 300 identified patients, most are descended from families from Quebec's Charlevoix-Saguenay region. It is estimated that 1 in 22 people in that region are carriers.

Based on the gene sequence discovered, it is possible that the encoded protein could play a role in "protein folding," a phenomenon believed to be involved in the integrity and survival of nerve cells.

"There are no immediate implications [of this discovery] for ARSACS patients," Dr. Thomas Hudson of McGill's Montreal Genome Centre told *CMAJ*. "We hope the next steps, aimed at understanding how the gene causes the disease, will help researchers derive new therapies to control or delay symptoms. But it is premature to envisage gene therapy. Family members of ARSACS patients can have access to a DNA test, to know their carrier status. This may have limited use in the area of prenatal counselling."

The Charlevoix-Saguenay-Lac-Saint-Jean region of Quebec is demographically isolated and is known internationally for its genetic anomalies.

Many of the region's 330 000 inhabitants trace their lineage to European founders who settled there during the 17th and 18th centuries. "Although I can deduce the existence of the ARSACS founders based on our DNA analyses, I don't know who they are," Hudson says.

Other genetic disorders that have been studied in the region include autism, hemochromatosis, oculopharyngeal dystrophy, subacute necrotizing encephalomyelopathy (Leigh's syndrome) and tyrosinemia.

Last year, a paper by investigators at

the University of Quebec's Chicoutimi campus studied inbreeding in the genealogies of 205 patients with autopsy-confirmed Alzheimer's disease (*Genet Epidemiol* 1999;16[4]:412-25). This study found that those with histories of Alzheimer's disease were significantly more inbred than a control group. The Alzheimer's disease was "explained by the high level of inbreeding of a few cases whose parents were related at the first-cousin level." Another 1999 study traced 120 living patients with bipolar disorder in the region, confirming linkages related to chromosome 12q23-q24 (*Am J Med Genet* 1999;88(5):567-87). — *David Helwig*, London, Ont.

Briefly . . .

Worst asthma symptoms caused by prostaglandin D₂

The mechanism behind asthma is under increasing scrutiny. In asthma, environmental antigens trigger immunoglobulin E antibodies, which then activate mast cells. These mast cells release substances that induce inflammation. Experiments with genetically engineered mice now show that one of these inflammation-inducing substances — prostaglandin D₂ — is responsible for the worst symptoms of asthma (*Science* 2000;287:2013-7). When the gene for prostaglandin D₂ receptors was removed from asthmatic mice, they did not experience the hyper-reactive airways typical of asthma. Future therapies targeting prostaglandin D₂ could mitigate asthma's life-threatening complications.

Pathologic protein gives fruit flies Parkinson's disease

Researchers have created fruit flies with Parkinson's disease — one of the few animal models of the disease, and proof that a mutant protein leads to the neural degeneration in the disease (*Nature* 2000;404:394-8). They now hope that the flies will show how the protein works, and provide a testing ground for new therapies. The researchers genetically engineered *Drosophila melanogaster* to express mutated α -synuclein, a protein found in abundance in nerves, whose function is unknown. Two mutations in genes that encode α -synuclein were recently found in families with inherited Parkinson's disease, leading to research into the protein. The fruit flies with mutated proteins have physical signs of Parkinson's disease — progressive loss of dopamine-secreting neurons and intracellular aggregates resembling Lewy bodies — as well as behavioural characteristics. The flies failed a standard vial-climbing test, indicating locomotor defects.