NEUROSCIENCE

A Mitochondrial Alzheimer's Gene?

Researchers have known for years that energy metabolism is abnormally low in the brains of patients with Alzheimer's disease (AD). Now, a team led by Robert Davis, at the San Diego biotech company MitoKor, and neurologist W. Davis Parker, of the University of Virginia School of Medicine in Charlottesville, offers a possible genetic explanation: Most AD patients seem to have inherited high levels of a mutant form of cytochrome oxidase (CO), a mitochondrial enzyme that is a key part of the cell's energy-producing machinery.

The finding, which is reported in the 29 April issue of the *Proceedings of the National Academy of Sciences*, could lead to a diagnostic test for the disease. Beyond that, it supports earlier suspicions that poor energy metabolism may contribute to the neurodegeneration that occurs in AD. Indeed, Alzheimer's researcher Bruce Yankner of Harvard Medical School calls the result "by far the strongest evidence" yet that a CO defect is involved in triggering the disease.

The current work is an outgrowth of Parker's 1990 discovery that CO activity is low in the blood platelets of AD patients. Subsequent studies also found low CO activity in Alzheimer's brains. The enzyme is there, but it doesn't work correctly, which suggests that it might be mutated, says Parker.

Three of the 13 proteins that make up the CO molecule are encoded not in the nucleus, but in the mitochondrial DNA. The team looked at those genes, as studies have shown that children of mothers with AD are more likely to get the disease than are children of affected fathers. That suggests a mitochondrial gene could be causing a predisposition to AD, as virtually all of the thousands of mitochondrial genomes we inherit come from our mothers.

The team found a relatively common variant of the mitochondrial genome in which two of the CO genes are consistently mutated. The variant turned up both in AD patients and normal controls, but it made up a higher percentage of the mitochondrial genomes in the patients: In 60% of the 506 AD patients examined, more than 20% of their mitochondrial genomes had the mutant form, while only 20% of the 95 controls (normal subjects and people with other neurological diseases) had mutation levels that high. One-fifth of the AD patients had mutation levels of 32% or more, higher than any controls. MitoKor is creating a diagnostic test based on the mutation assay.

The team showed that these CO gene mutations have physiological effects by transferring mitochondria from AD patients into cultured cells that lack mitochondrial DNA. The resulting cells had impaired energy production, reflected by their high production of oxygen free radicals, the damaging molecules produced when energy-generating processes don't run to completion.

The findings could provide several links with other areas of AD research. Free radicals, which damage cell membranes, have been implicated in the destruction of neurons in Alzheimer's. And 4 years ago Yankner and his colleague Dana Gabuzda linked CO activity to another possible cause of AD: They poisoned CO in cultured cells and found an increase in a direct precursor of β amyloid, the protein that forms the core of the senile plaques found in the brains of AD patients.

The new work falls short of proving that CO mutations help cause AD, but the idea deserves to be explored, says Yankner: "It is not an area that has attracted a great deal of attention in Alzheimer's research, but it might now."

–Marcia Barinaga

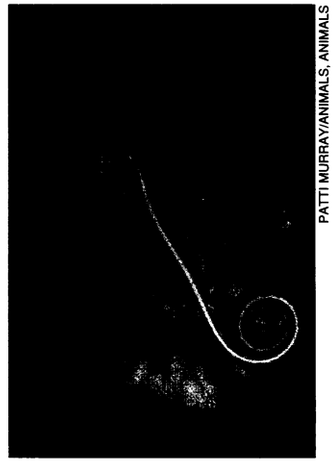
EVOLUTIONARY BIOLOGY

Catching Lizards in the Act of Adapting

When evolutionary biologists transplanted small populations of *Anolis sagrei* lizards from Staniel Cay in the Bahamas to several nearby islands 20 years ago, they thought that the reptiles would go extinct. Indeed, that was the outcome the researchers planned to study. But instead of expiring, the small brown lizards, like Oklahoma land-rush settlers, flourished—even though their new homes differed dramatically from their original island. And the "extinction" study turned into a demonstration of evolution in action.

In the current issue of *Nature*, Jonathan Losos of Washington University in St. Louis and his colleagues report that the transplanted lizards appear to be in the first stages of an adaptive radiation, undergoing the kind of body changes needed to inhabit a new environment. Such changes could in time turn each island's population into a separate species—the same process that led to the great diversity of finches that Darwin spotted on the Galápagos Islands, and to the galaxy of *Anolis* lizards themselves (150 species in the Caribbean alone). In particular, the researchers saw the lizards' hindlimbs grow shorter, an apparent adaptation to the bushy vegetation that dominates their new islands.

The change was rapid, but others have also demonstrated the speed with which organisms can adapt in the wild (*Science*, 28 March, pp. 1880 and 1934). More important, by drawing on previous studies of anole adaptations, the Losos team was able to predict precisely how the lizards' bodies would change in response to their new homes. The leg-length change they observed might not be genetic, some researchers note; it could be environmental—the equivalent of a body-builder's muscles. But if it is rooted in the genes, then the study is strong evidence that isolated populations diverge by natural selection, not genetic drift, as some theorists have argued. "It's the first attempt to make a prediction about how the theory of evolution will work—and then show that it does happen as predicted," says University of California, San Diego, evolutionary biologist Trevor Price.



PATTI MURRAY/ANIMALS, ANIMALS

Reptile moves. New home leads to shorter legs in *Anolis* lizards.

Once Losos and his colleagues realized that their transplanted lizards were surviving instead of becoming extinct, they decided to study how they were adapting. They focused on how the habitat change affected the length of the animals' hindlegs because Losos had previously demonstrated that the trait correlates with the lizards' preferred perch. For instance, species living on tree trunks have longer legs than do those living on twigs, apparently because they can trade the agility that comes with shorter legs—crucial on bushy vegetation—for the increase in speed that longer limbs provide. Because Staniel Cay, the home of the founding population, is covered with scrubby-to-tall forest, the anoles there are long-legged.

But the 14 lizard-free islands that the researchers seeded with the Staniel Cay pioneers have only a few trees; most of their vegetation is bushy and narrow-leafed. "From the kind of vegetation on the new is-