Gene defect for muscle disorder identified

Since 1982, a small cadre of scientists has gathered family histories of people with early-onset torsion dystonia, a crippling disorder that causes the muscles to contract, twist, or sometimes jerk involuntarily. The researchers also took blood samples from the families and painstakingly probed their DNA for genetic clues that might reveal dystonia's origin.

There were few other options. Unlike neuromuscular diseases such as Parkinson's or Huntington's, dystonia is difficult to track in the body. "There is no part of the brain that degenerates [in dystonia], so there is no easy way to see what's going on," says Laurie J. Ozelius, a geneticist at Harvard University Medical School in Boston.

Their efforts have now paid off. Ozelius and her colleagues report in the September NATURE GENETICS the discovery of a mutation that underlies the disease. It's in a gene named *DYT1*.

The researchers examined blood samples from 267 unrelated people with no history of severe dystonia and from members of 68 families with clear symptoms of the disorder. The mutation appears in none of the control group and in all of the dystonia patients' families.

Ozelius and her collaborators also identified a mysterious protein, torsinA, which the *DYT1* gene encodes. A defective version of torsinA predisposes a person to dystonia.

If one parent has the disease, which is genetically dominant, each child should have a 50-50 chance of inheriting it. Yet researchers were puzzled for years because fewer than half of the children showed symptoms of dystonia. Indeed, recent work reveals that only 30 to 40 percent of people with a mutated *DYT1* ever show its effects.

This oddity led researchers to suspect that environmental factors combine with the mutation to trigger the disease. The answer may lie in the role of torsinA. While the protein's function is unclear, scientists see links between it and known actors in the cell. For example, torsinA resembles compounds called heat-shock proteins, which are expressed when a cell faces fever or injury.

Researchers now plan to reexamine family data from carriers of the mutated gene. Many such families report incidents of trauma or high fever in a youngster who later developed severe dystonia, says study coauthor Susan B. Bressman, a neurologist at Columbia University. However, since virtually all young children encounter such stresses, the researchers don't know whether a connection will emerge.

An age-related decline in the risk of symptoms also poses a puzzle. "Once you reach the age of 22, you're generally home free," Bressman says.

The fact that dystonia doesn't strike in later adulthood raises biological questions, she says. Does the body do something to block the mutation in later years, or does the mutation have a time-dependent shutoff switch?

"It's a fascinating discovery. It will whet the appetite of neuroscientists," says Giovanna Spinella of the National Institute of Neurological Disorders and Stroke in Bethesda, Md.

The *DYT1* mutation is rare, occurring in no more than 1 in 5,000 people in the United States. Among Jews of European descent, it occurs in as many as 1 in 1,000 people, Bressman says.

The discovery of the mutation opens the way for a simple test to distinguish a child with severe dystonia from one with cerebral palsy or one of several milder types of dystonia. Severe dystonia is seldom fatal, but it can render an individual wheelchair-bound.

Future research will involve rodents with and without mutated *DYT1*, Ozelius says. Researchers in the laboratory will also be able to expose tissue cultures with and without the mutated gene to hot temperatures and stress to determine whether torsinA behaves like a heat-shock protein. *—N. Seppa*

Well-groomed rodents stay cool, calm

Some young rats take a maternal licking that keeps them ticking by developing an ingrained sense of curiosity and physiological calm under duress. Others, a new study suggests, are literally groomed to react with heightened sensitivity and alarm to new and potentially threatening situations.

These findings emphasize the power of the early social environment to mold individual responses to stress, at least in animals capable of inhabiting surroundings that pose an array of survival challenges. For the rats under study, a mother's natural style of caring for her offspring may tailor their stress reactions to suit the challenges they will most likely encounter as adults, contends a team of neuroscientists headed by Michael J. Meaney of McGill University in Montreal.

Meaney's group drew inspiration from a 40-year-old study in which newborn Norway rats, taken from their mothers by a scientist for 15 minutes daily during the first few weeks of life, excreted low amounts of certain stress hormones when under threat and explored new surroundings with gusto, compared to nonhandled pups. Mothers fervently licked and groomed the handled pups, but the significance of that behavior eluded the scientists.

The new experiment, described in the Sept. 12 SCIENCE, finds that rat moms spend about twice as much time licking and grooming offspring that have been removed daily by a handler during the 3 weeks after birth. Moreover, about one in three mothers of nonhandled pups lick and groom at that higher rate, Meaney and his coworkers report.

As adults, the recipients of the exuberant licking and grooming display signs of a reduced responsiveness to stress, the scientists hold. For instance, these animals exhibit low concentrations of adrenocorticotropic hormone and corticosterone—two stress hormones—after being restrained briefly while researchers collected blood samples. In addition, cells in a crucial part of the animals' brain, known as the hippocampus, show responses associated with efficient regulation of another stress hormone, glucocorticoid.

Moreover, adult rats that had experienced vigorous licking and grooming as pups explored open spaces with particular ease and possessed an abundance of brain receptors for a class of anxiety-reducing substances called benzodiazepines.

Norway rats inhabit many ecological niches, each of which may help to shape mothering practices and, as a result, the stress responsiveness of succeeding generations, according to the researchers. One possibility is that mothers that must leave their pups briefly to store and retrieve food tend to lick and groom them with particular vigor, rendering the offspring better able to cope with short separations.

The findings may apply to humans, since we also live in a vast spectrum of environments, the scientists add.

"This current study must spur on work examining how early experience alters the trajectory of [human] development," writes Stanford University biologist Robert M. Sapolsky in an accompanying comment.

Indeed, exposure to touch provides crucial sensory support in the development of human infants. Researchers have noted significant gains in weight and physical health in premature babies given gentle massages while in the hospital.

Further rodent research needs to examine whether even subtler individual differences in mothering style exist, Sapolsky says. Investigators can then explore how these differences trigger neurotransmitter and receptor changes in pups' brains. *—B. Bower*