DNA Repeats Tied to Neuromuscular Diseases

Just two years ago geneticists thought they had fingered a unique genetic mistake as the cause of a disease called fragile X syndrome (SN: 6/8/91, p.359). Since then, researchers have traced three more disorders, including myotonic dystrophy (SN: 2/15/92, p.102) and Huntington's disease, to similar mistakes. Now, the discovery that this kind of mistake – unusual repetition of a short stretch of DNA – leads to yet another neuromuscular disorder has driven home the idea that such errors may account for many genetic disorders of the nervous system.

After decades of searching, two geneticists and their colleagues have demonstrated that chromosome 6 in people with spinocerebellar ataxia 1 contains a short piece of DNA that repeats 40 to 80 times, two to four times more than it should. These excess repeats lead to a progressive destruction of part of the brain, which causes a loss of coordination and, eventually, loss of the ability to breathe or swallow, says Huda Y. Zoghbi, a pediatric neurologist at Baylor College of Medicine in Houston. She, Harry T. Orr of the University of Minnesota in Minneapolis, and their colleagues describe their findings in the July NATURE GENETICS.

Four chemical entities called nucleotides make up the genetic alphabet, spelling out the words and sentences – known as genes – that specify the amino acid sequence of each protein. In some mutations, the loss or substitution of nucleotides in a gene creates words that make no sense, which results in an inactive protein or none at all getting made. But in this ataxia and the other four genetic disorders, the mistake arises when a series of three nucleotides repeats many times more than usual. That error can spell out a new "word" that leads to the creation of an atypical, potentially harmful protein, Zoghbi says.

"I'm sure there are going to be other diseases found to have this mechanism," predicts human geneticist Stephen T. Warren of the Howard Hughes Medical Institute at Emory University in Atlanta.

Orr and Zoghbi found the repeats by examining pieces of the million-base-pair section of chromosome 6 known to be defective in people with this ataxia. They made enough kinds of short, 20-nucleotide fragments to cover all possible repeating threesome combinations. Then they evaluated each repeating section of DNA to see which section varied in the number of repeats in people with the disease. The threesome that repeats involves the nucleotides cytosine, adenine, and guanine.

The number of times this threesome repeats varies from one generation to the next, Orr and Zoghbi say. They observed that older family members with less severe disease had about 40 repeats, but the gene in some of the children contained 80 copies of the three nucleotides. These children developed symptoms much earlier in life. "The bigger the expansion, the more severe the disease," Zoghbi says.

This variability could explain why many so-called genetic diseases fail to appear to the same degree in every generation or family member, says Warren. Previously, researchers thought several genes interacted to cause these baffling disorders, making the identification of their genetic bases too daunting. "Now people are reexamining these disorders," he adds. "And there are a slew of diseases like that."

For example, two other reports in the July NATURE GENETICS pinpoint the DNA responsible for two other types of ataxia. In one paper, Japanese researchers tracked the faulty gene leading to Machado-Joseph disease, which causes nerve and muscle degeneration, to chromosome 14.

In the other, collaborators in England, Cuba, France, Germany, and the United States studied 450 Cubans and seven French families. In those people, spinocerebellar ataxia 2 arises from aberrations on chromosome 12, says Sue Chamberlain of St. Mary's Hospital in London, one of the researchers. Their data suggest that a third type of this ataxia may also exist.

Data from families with these ataxia disorders indicate that one generation suffers mild symptoms as adults while the next generation develops more severe disease, often during childhood. "We would suspect very strongly that those mutations will be unstable trinucleotide repeats," says Orr.

"This commonality [of abnormal repeats] is very exciting," comments Giovanna M. Spinella, a clinical neurologist at the National Institute of Neurological Disorders and Stroke in Bethesda, Md.

Still, many questions remain. The genome contains many sequences of DNA in which two, three, or four nucleotides repeat a half dozen times or more. Scientists do not know why the number of repeats suddenly becomes variable or why excess threesomes, but not twosomes or foursomes, cause problems, especially for the nervous system.

"We have a lot to do now to try and link the pathology [of these diseases] with these repeats," Spinella says. – *E. Pennisi*

Ballast-water invaders pose ecological risk

They came, they multiplied, they conquered: In the mid-1980s, zebra mussels hitchhiked to the Great Lakes in the ballast tanks of a transoceanic cargo ship, triggering one of the most disastrous ecological invasions in recent U.S. history. But other ballast-water invaders are reaching saltwater ports, inland waterways, and marine estuaries on a vast and largely unnoticed scale, says marine ecologist James T. Carlton of Williams College in Williamstown, Mass.

Carlton and colleague Jonathan B. Geller of the University of North Carolina at Wilmington counted and identified the creatures residing in the ballast water of 159 ships in Coos Bay, Ore., one of the largest exporting ports in the Pacific Northwest. Water from the ships, which hailed from 25 Japanese ports, contained 367 different marine species, including shrimps, sea anemones, jellyfish, snails, clams, fish, flatworms, and a variety of microscopic life forms, Carlton and Geller report in the July 2 SCIENCE.

"The total diversity was a surprise," Carlton recalls. "We didn't expect to find things like hermit crabs, starfish, or sea squirts."

Since the 1880s, empty and near-empty ships have taken on water as ballast to increase their stability and balance on the open seas. After reaching their destinations and loading cargo, freighters pump the water back out – along with any marine life sucked up into the tanks at the home port.

Dumping ballast water into foreign ports could have dire consequences for native marine creatures and for the people whose livelihoods depend upon them, says Carlton. "All you have to do is insert one new species into a system and the ecological roulette [wheel] is set in mo-

Jeff Goddard/University of Oregon

This scale-worm larva traveled to Coos Bay, Ore., in the ballast water of a Japanese freighter. Such nonindigenous invaders pose ecological hazards to bays, estuaries, and inland waterways on a global scale, researchers say.