Wrenching genes
New insights into a rare disorder may illuminate the biology behind a range of mental problems

By Nancy Shute

Lindsey Ross loves making chocolate chip cookies and playing PlayStation—the usual stuff for a miniskirted 15-year-old. But Lindsey’s life is anything but usual. The Schaumburg, Ill., teenager’s hands flap uncontrollably, and words come out of her mouth as shrills. She communicates with her family and high school friends with an electronic voice synthesizer.

It wasn’t always this way. As a toddler, she chattered away happily. Then, one by one, the words started disappearing at age 2½. After dozens of tests failed to explain the decline, a neurologist finally diagnosed Rett syndrome.

Just a few years ago, Rett syndrome was an obscure neurological disorder known only to a handful of scientists. It was often mistaken for autism since children with Rett appear to develop normally for the first six to 18 months of life. It wasn’t until 1983 that it was widely recognized as a separate disorder that affects 1 in every 15,000 children. Symptoms include seizures, loss of motor control, digestive and breathing problems, and perhaps mental retardation—though victims’ mental abilities are hard to test. Many also share a strange gesture, wringing their hands over and over.

Three years ago, researchers found that a single genetic mutation causes most Rett cases. Intriguingly, the same gene mutation has since been identified in some people with schizophrenia, bipolar disorder, and forms of autism, raising the possibility that identification of the Rett gene could speed understanding of these far more common diseases. This month, Baylor University neurologist Huda Zoghbi reported in the journal Neuron that her research team has succeeded in creating a Rett-like disease in mice. “This gives us the freedom to try therapies we wouldn’t dare try in humans,” says Zoghbi, who also identified the Rett gene. If Rett patients were identified at birth, the disorder could perhaps be treated early.

Spectrum. Finding specific genes that cause diseases is frustratingly difficult, but Rett made a good candidate for a gene hunt because it primarily affects girls. Researchers started looking for a gene on the X chromosome, but it was still a needle-in-a-haystack exercise because the disease appeared to result from a random genetic mutation. Then they discovered the Woodcock family of Union, Wash. Both Maureen Woodcock’s daughter Erika and granddaughter Paige have Rett, and when researchers studied the DNA of the extended family they found that Rett was indeed inherited.

What’s more, they found that Paige’s mother, Tiffany, had the same mutation—but only mild learning disabilities. Something was clearly modulating the bad DNA in her body. The gene that is mutated in Rett helps switch DNA on and off, which may account for its broad range of effects in various disorders. The fact that girls have two X chromosomes also plays a role; only one X is activated, so each cell has a fifty-fifty chance of getting the mutant gene.

The Woodcocks made one more contribution to science, a tragic one. When Tiffany became pregnant again, the family was thrilled to learn that the baby would be a boy: no boy had ever been diagnosed with Rett. But little Aridied just after his first birthday. He, too, had the Rett gene. It’s now clear that boys do have Rett. But because males have only one X chromosome, the disease is invariably fatal. “I believe my girls and grandson have an important job to do,” Maureen Woodcock says. “Through them, the research value of our family will live on.”

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