ministries, such as the well-regarded National Institute of Mental Health and Neurosciences in Bangalore.

India has a special opportunity to contribute to the field of neural imaging, says Vijayalakshmi Ravindranath, a neurochemist in line to be director of the center, by carrying out large-scale functional mapping studies on so-called "drug-naïve patients," those with neurological disorders who have not yet received treatment. Supporters acknowledge that it will be a while before the center can hope to enter the front ranks of global science, however. "Catching up is a Herculean task, and it may take another 20 years," says Prakash Narain Tandon, a neurosurgeon at the All India Institute of Medical Sciences in New Delhi. But they argue that creating the center is an important, and necessary, step.

India is already looking for international collaborators. About 250 scientists from five countries are participating in a Colloquium on Brain Research here this weekend to showcase the new center, and Richard Nakamura, deputy director of the U.S. National Institute of Mental Health, is heading a delegation that expects to sign a memorandum of understanding for future collaborations and scientific exchanges with NBRC. The center also hopes to link up with Japan's Brain Science Institute at the Institute of Physical and Chemical Research (RIKEN), outside Tokyo. "India is not without promise in the neurosciences," says Nakamura. "Indian scientists have always done very well in the U.S. because they are well trained and do not face a major language barrier. By setting up strong centers within India, this brain drain can be slowed, and talented scientists can help develop the economy of India and work to improve the health of its people."

The center is currently housed in temporary quarters at the International Center for Genetic Engineering and Biotechnology. Work is under way on a new home in Gurgaon, about 35 kilometers outside Delhi, where an unused vaccine laboratory built several years ago is being renovated.

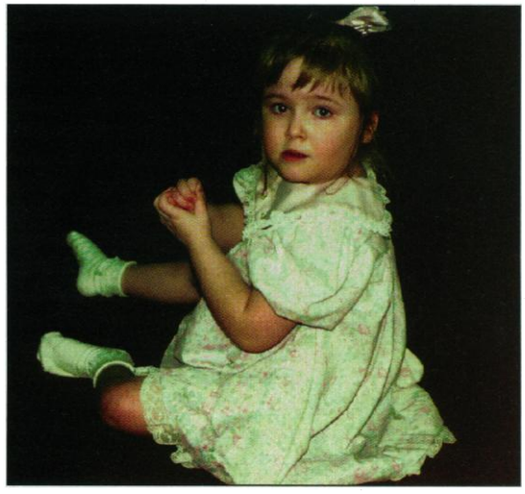
–PALLAVA BAGLA

HUMAN GENETICS

Gene Defect Linked to Rett Syndrome

As the parent of a child with Rett syndrome, Patty Campo describes the genetic disease as "a horrific nightmare." Second only to Down syndrome as a cause of female retardation, Rett syndrome left Campo's daughter, who appeared normal at first, unable to stand, talk, or use her hands by age 5. Now, a team led by pediatric neurologist and geneticist Huda Zoghbi of Baylor College of Medicine in Houston may have tracked down the gene at fault in Rett syndrome, which afflicts at least one in 10,000 girls.

In the October issue of *Nature Genetics*, Zoghbi, Uta Francke at Stanford University in California, and their colleagues report that mutations in a gene called *MeCP2* cause nearly a third of the Rett syndrome cases they studied. The protein encoded by the gene is known to help "silence," or shut down, other genes that have been tagged with a methyl group during development. The group's work is the first to link a human disease to a defect in this process, says geneticist Brian Hendrich, who co-authored a News and Views editorial on the work.



Early sign. Excessive hand-wringing is one of the first symptoms displayed by girls with Rett syndrome.

CREDIT: HHMI

Exactly how the defect leads to the neurological decline of the afflicted girls has yet to be deciphered. Still, geneticists say they welcome the discovery. "*MePC2* silencing, which underlies the defect, is not only fascinating in its own right," says Huntington Willard of Case Western Reserve University in Cleveland, Ohio, "but the discovery of its link to Rett syndrome also opens all kinds of doors to new [research] avenues" that might lead to a treatment.

Although at least a half-dozen labs pursued the Rett syndrome gene, the hunt stretched out into decades. Geneticists normally locate disease genes by studying how the disease is inherited in afflicted families. But Rett syndrome rarely seems to run in families, and even when the mutation is passed down in a family, it is often hidden.

One problem is that males who inherit the mutation, which affects a gene on the X chromosome, usually die before or shortly after birth, presumably because they do not have a second copy of the X chromosome that might compensate for the defective one. In contrast, females carry two X chromosomes. But their cells randomly inactivate one to avoid overproducing proteins encoded by X chromosome genes, and so a female may not have symptoms unless more than half her cells express the bad gene.

Despite these hindrances, Zoghbi's group found two families with more than one affected member and Stanford's Francke found another. They combined their samples to help Zoghbi narrow down the location of the Rett syndrome gene to a region around the q28 segment of the X chromosome. In addition, Eric Hoffman of the University of Pittsburgh also had evidence that the gene is located in Xq28. To pinpoint the gene, Zoghbi then turned to what she terms "a brute-force way."

She scrolled through databases to identify all the known genes in Xq28—at least 100 candidates, she notes—and then sequenced the versions carried by the patients and compared their DNA to that of unaffected individuals. After more than a dozen failed tries, her team hit pay dirt with the *MeCP2* gene, which had been cloned in 1992 by geneticist Adrian Bird's team at the University of Edinburgh in the U.K.

Still, many questions remain. The gene was mutated in only three of eight affected family members and in five of 21 spontaneous cases, raising the possibility that mutations in other X chromosome genes might also cause the disease. Zoghbi offers another possible explanation: Her team only scoured *MeCP2*'s protein-coding regions and so might have missed mutations in regulatory regions that affect the gene's expression.

Even more mysterious is how mutations in one gene involved in the silencing of other genes could cause the myriad of Rett syndrome defects. "We really don't know the answer to that," says Zoghbi, although she and others have several ideas. One is that a failure of *MeCP2* to prevent excess gene expression results in genetic "noise" that harms the brain, in particular.

Studying *MeCP2* function in patients' cells and analyzing the defects in mice that have had their *MeCP2* genes knocked out could yield some answers. Bird and his colleagues have already made knockout mice and found, consistent with what's already known about Rett syndrome, that male mice without a functional *MeCP2* gene die before birth, while females that have one bad copy of the gene may develop symptoms similar to Rett's. Only after learning the targets of the *MeCP2* defect, Zoghbi says, "can one start thinking about treatments."

–TRISHA GURA

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