Catching up with Canavan's

Genetics of spongy brain disease hints at needs of white matter

By GABRIELLE STROBEL

Five years ago, Reuben Matalon began to lift the veil of obscurity shrouding Canavan's disease, a fatal brain disorder that afflicts mostly Jewish children of Eastern European ancestry. He first pointed to a small molecule as the likely biochemical culprit. Now, Matalon, a physician and molecular biologist at the Research Institute of Miami Children's Hospital, and his co-workers have cloned the gene underlying the disease, unraveling its DNA code and discovering a mutation that occurs in 85 percent of all cases studied.

The group's finding, reported in the October NATURE GENETICS, paves the way for devising prenatal tests and DNA screens for parents who fear they may carry the mutation. In addition, it holds tantalizing clues to related brain disorders and opens new avenues for understanding the biology of the brain's white matter.

"Matalon deserves a great deal of credit," says neurologist Hugo W. Moser at the Kennedy Krieger Institute in Baltimore, "because he has taken the story of that dreadful and mysterious illness all the way from connecting it to a biochemical abnormality to the final point of identifying and cloning the gene."

Canavan's disease, also called spongy brain degeneration, strikes one in roughly 3,500 children in the Ashkenazic Jewish community and one in 30,000 to 40,000 children in other populations, estimates Matalon. The disease destroys myelin, the insulating sheath surrounding nerve cells. The myelin disintegrates so thoroughly that the brain's electrical signals cannot sweep along nerve processes properly, thereby thwarting the development of virtually every function controlled by the nervous system. Although the condition manifests itself early, it is difficult to diagnose. Children with Canavan's cannot sit, walk, or talk, and most die before the age of 5.

While no cure for Canavan's is on the horizon, this study will help in efforts to develop a DNA test that will speed up diagnosis. Testing for the mutation in adults and fetuses may become possible in a few years, says Matalon.

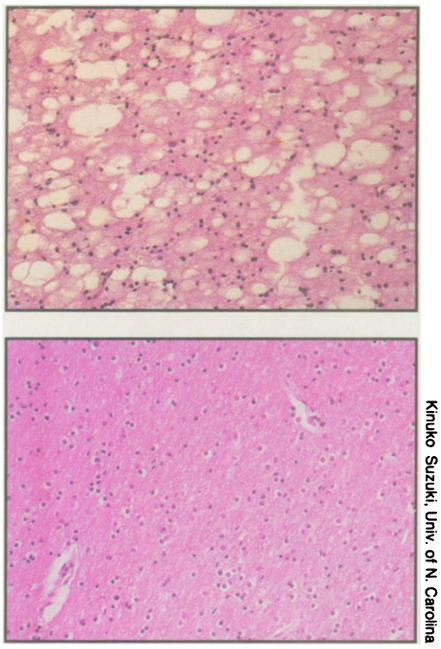
Although such a test is already available to some families with affected children, further research is needed before such a test will prove reliable in a wider population, Matalon cautions. Researchers need to pinpoint enough mutations to account for at least 95 percent of Canavan's cases. They are close to that goal: So far, Matalon's group has found two mutations that together account for 92 percent of the examined cases, and they are working on two more, he says.

"One [of these mutations] alone occurs in 85 percent of all cases we have looked at. We have traced it back through pedigrees of affected families, and we assume that it originated in a Lithuanian group, from where it was transmitted through the Jewish community," he explains. Recessive diseases like Canavan's can persist in a population even though affected individuals never reproduce. That's because people who carry only one mutated gene are healthy, but may pass that gene on to their children. A child who inherits two defective genes will develop the disease.

The mutation that causes most Canavan's cases is a tiny, but devastating flaw: Of the thousands of nucleotides, or units of genetic code, that make up the Canavan's gene, only one is different, the researchers report.

Having found that minuscule DNA difference helps researchers understand exactly what goes wrong in Canavan's children, Matalon says. The mutation plants a misfit amino acid into the gene product, an enzyme called aspartoacylase. The researchers suggest that this misfit is located in the so-called active site of the enzyme. There, it would paralyze aspartoacylase, making it impossible for the enzyme to catalyze an important biochemical reaction. That reaction converts N-acetyl-L-aspartic acid (NAA) and somehow holds the clue to Canavan's disease and possibly other, related myelin diseases as well, Matalon says.

In 1988, his group found excessively large amounts of NAA in the brains of Canavan's patients and identified aspartoacylase deficiency as the possible cause of the disease. "That was a huge step forward, because Canavan's has been a complete mystery since its first description 60 years ago," says Moser. The disease still poses riddles, though: "NAA is a constituent of neurons [which make up the brain's gray matter], yet it is involved in diseases of the white matter."



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Numerous vacuoles characterize the degenerating white matter of a patient with Canavan's disease (above). In contrast, the white matter of healthy brain tissue appears continuous (below).

Matalon suggests that NAA may play a role in a chemical communication system between neurons and the white matter, informing the myelin that all is well in the neuron and thus maintaining the integrity of myelin. The neuron produces NAA but not the enzyme that converts NAA, whereas the white matter manufactures the enzyme, the researchers report. "Why is that? I think it is to allow NAA to travel down the axon, from where it enters the white matter," Matalon says. There, the enzyme breaks down NAA, and the products of that reaction somehow help maintain myelin, he adds. Without the enzyme, NAA piles up, its reaction products never appear, and the myelin degenerates, he reasons.

These new insights into the metabolism of myelin pose intriguing questions. In other diseases of the white matter, and in multiple sclerosis, Huntington's chorea, and AIDS, concentrations of NAA are too low. In Canavan's, the NAA concentration is too high, suggesting that NAA must be adjusted to a certain level if myelin is to stay in healthy contact with nerves, Matalon says. Moser notes that while details of this hypothesis are still speculative, "we can soon expect more to come as researchers develop an animal model for this terrible disease." □