

From Health to Huntington's

Tracking the disease's earliest symptoms to discover why nerve cells die

BY GINA SHAW

Nearly a decade later, Karen Milek remembers every little detail of the day she learned that she will develop Huntington's disease.

Shortly after her mother died of the degenerative disorder in 1997, Milek had decided to get tested for the Huntington's gene. Upon learning she'd tested positive for the gene, she did the craziest thing she could think of: buying a \$70 Ralph Lauren T-shirt. "That was as dramatic as I got," she says. "Then I said, 'Where do I sign up for a study?'"

So Milek, now 45, travels from her Winter Park, Fla., home to the University of Iowa every year for a full day of testing in a clinical trial. The exhausting annual regimen includes blood sampling, MRI scanning, survey questions, neuropsychiatric exams, neurological motor exams and a sophisticated cognitive science assessment.

Why take the time to undergo all these tests over and over again—tests that she's unlikely to benefit from personally—when she knows that she's already living on borrowed time?

"This is why I'm living," explains Milek, who's become a Huntington's advocate, traveling to London and Paris for research and conferences. "I've found a way that I can help other people. This study is so important, because it's about finding out the things that can tell you that this disease is starting before it becomes obvious."

Milek decided to get tested for the Huntington's gene because each person who has had a parent afflicted by Huntington's disease is born with a 50-percent risk of inheriting the faulty gene, which will inevitably lead to the full-blown disease. Her younger sister, who has likewise tested positive for the Huntington's gene, is also participating in the study, while their older sister and their brother have elected not to be tested.

The study, called PREDICT-HD, is one of the largest and most ambitious studies undertaken to date in people who have tested positive for the Huntington's gene. It's designed to address a critical gap in scientists' understanding of Huntington's disease: even if an effective treatment were to magically appear tomorrow, doctors wouldn't know when to start giving it to their patients.

Although the symptoms of Huntington's—a degenerative brain disease that,

dead or severely damaged, probably beyond repair, by the time noticeable symptoms develop.

"The best chance of treating the disease is when the neurons are just sick, not gone, so ideally you would want to begin a treatment *before* there has been serious decline in function," says the study's principal investigator, Jane Paulsen, Ph.D., a neuropsychologist and Huntington's expert at the University of Iowa. "Someday, we will find a compound to slow the progression of this disease—but when should we start giving it?"

That's one of the central questions Dr. Paulsen hopes to answer with her study, now in its fifth year at its 32 international research sites.

Among the study's goals:

- ▶ To determine what the earliest signs of Huntington's are and when they begin.
- ▶ To determine what the most accurate tests are that clinicians can use in detecting the onset of Huntington's.
- ▶ To determine what factors influence the age at which a person carrying the Huntington's gene develops the illness.

Ultimately, Dr. Paulsen hopes, the study will provide essential information for future clinical trials of experimental drugs to treat Huntington's. "Right now, we can measure Huntington's disease progression once you're sick: Can you drive? Can you walk without falling? Can you feed yourself?" she says. "But we don't have reliable measures that would prove that an experimental compound could slow the disease in the 'pre-diagnosed' state. And the Food and Drug Administration would never approve a 'pre-diagnosis' drug without this information."

The information being gathered through the study becomes even more important in light of recent studies in genetically modified mice. Those studies show



RACING FOR A CAUSE Karen Milek competes in marathons and Huntington's disease triathlons "as a challenge against HD."

over the course of about 10 to 20 years of progression, diminishes the ability to walk, think, talk and reason—typically begin between the ages of 30 and 45, scientists believe that the neurobiological and neurobehavioral changes involved may start much earlier. With Huntington's, as with many brain diseases, half or more of the neurons in the affected parts of the brain are already

that turning off the defective Huntington's gene in the mice can put the brakes on the degenerative brain changes associated with the disease.

Gene therapy in mice is a long way from gene therapy in humans. But

if these promising early results can be transferred to humans, scientists will still need to know when they should start the gene therapy. "It can't be done in utero or very soon after birth, because the same gene that's associated with Huntington's disease is critical for neurodevelopment in early life," says Dr. Paulsen. "There could be dire consequences if you turn the gene off too soon. So if gene therapy becomes a possibility, when do you initiate it? The only way to answer that question is with a study like this."

For a Grand Rapids, Mich., woman named Deb (who's asked that her surname not be used because of insurance-coverage worries), this study is about one thing: her children.

"My kids are going to have to deal with this at some point," she says. "I don't want them to think Mom just sat on her butt and did nothing. I want them to know that at least I went out and tried to find drugs that would actually help."

The mother of two young sons, ages 3 and 4, Deb tested positive for the Huntington's gene while she was pregnant with her second son. Tested in utero, the little boy does not carry the gene. But because she did not know that Huntington's disease was in the family when she was pregnant with her first son (her father was diagnosed right after she gave birth), Deb didn't undergo prenatal testing with him. Ethically, the boy can't be tested for the gene now until he is 18 and old enough to consent himself.

For many who have inherited the faulty gene, study participation is about one thing: their children.

The study, funded by the National Institutes of Health with additional support from the High-Q Foundation, is already well ahead of recruiting expectations. "We already have over 800 study participants,"

says Dr. Paulsen, who expects to exceed 900. "Many people were concerned we would have difficulty recruiting. We're asking people who are currently healthy to take a day out of their lives, away from their families and jobs, to participate in a study for a disease that they already know they're going to get. But I've been so amazed at the strength and integrity with which these people come to the research, with their willingness to dive in. Even if it won't be for their generation, they want to try to do something for their children."

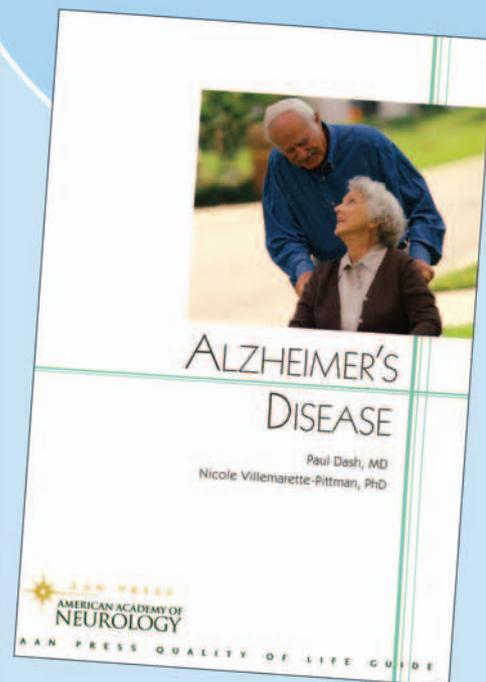
Although the study is ongoing, preliminary results are very exciting, says Dr. Paulsen. "It looks like the detection of disease is going to be readily apparent, using our measures, more than a dozen years before traditional diagnosis," she says. "We will be able to answer so many questions about the earliest stages of the disease that no one's ever looked at in any neurological disease to date."

Deb has just one message for people like her with the Huntington's gene: "If you have it, get involved. It's going to take those of us who are gene-positive and still young enough to help the researchers find a cure." NN

To find out more about the PREDICT-HD study, call 1-800-487-7671 or visit huntington-study-group.org.

For clinical trials listed in the AAN's journal *Neurology*, visit neurology.org/clinicaltrials.

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