

Jews and Parkinson's

A new study at Northwestern University looks at the links between the two in the hope of finding a cure

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Jane Spector lives in irony.

It's a cruel irony in many ways. The 70-year-old Chicago woman, an Ashkenazi Jew, has a genetic mutation that has been found to cause Parkinson's disease in some of the individuals who have it.

She doesn't have the disease. But her husband, Dr. Todd Davis, 72, has had it for close to 25 years. He is a convert to Judaism.

It was because of Spector's familiarity with the devastating effects of Parkinson's – the tremors, the halting gait, stiff muscles, slowed or even inaudible speech – that she was eager to join a new study seeking the gene mutation that was found to be present in her.

Her husband, a beloved pediatrician who had to quit practicing at age 53 due to the disease's progression, supported her decision.

They are both hoping that the research being done will lead to finding a cause and, eventually, a cure or prevention for the dreaded disease, which strikes millions of people, primarily older people, around the world.

A 2004 discovery by Dr. Susan Bressman and others at Beth Israel Medical Center in New York shook up the medical community, which had long believed that genetics played a relatively minor role in the development of Parkinson's disease.

The discovery: a mutation in a single gene, LRRK2, is a major cause of the disease among Ashkenazi Jews as well as North African Arab Berbers.

Mutations in the gene, researchers believe, account for 15 to 20 percent of Parkinson's in Ashkenazi (Eastern European) Jews. For people who have a sibling, parent or child with a LRRK2 mutation, the chance of also carrying the mutation is around 50 percent.

In the general population, less than two percent of Parkin-

son's patients are believed to harbor the mutation.

Having the LRRK2 mutation doesn't necessarily mean an individual will get the disease, which is progressive and may produce tremors, slowed movement, muscle stiffness, impaired posture and balance, speech changes and other symptoms. In fact, scientists estimate that only about a third of people with the genetic mutation will develop Parkinson's.

Scientists explain that the findings don't mean that Ashkenazi Jews, or members of any other population, have "bad genes." As with the BRCA1 and BRCA2 gene mutations for breast cancer and variants for such diseases as Tay-Sachs, the discovery simply means that certain diseases are more prevalent in certain populations due to centuries of members of those populations marrying others from the same gene pool.

Now the Michael J. Fox Foundation is launching a new phase of a study that began in 2010 and is actively seeking help from the Jewish community in Chicago and 31 other sites across the United States, Europe, the Middle East and Australia.

The Parkinson's Progression Markers Initiative (PPMI) is a clinical study designed to identify and assess biomarkers in people who may be at risk to develop Parkinson's. (Find out more about the study at www.michaeljfox.org/ppmi/genetics.)

A biomarker is a substance or characteristic in the body that is associated with the presence or risk of disease – think cholesterol for heart disease.

According to information about the study, "The discovery of a biomarker of Parkinson's disease is critical to the development of new and better treatments for PD, particularly treatments that could slow or stop the progression of the disease, something no currently available treatment can do."

The material goes on to note that identifying biomarkers in individuals who are at risk of developing PD could help researchers develop treatment at an early stage of the disease and

possibly delay or prevent the onset of symptoms.

In Chicago, the principal investigator for the study is Dr. Tanya Simuni, professor of neurology and director of the Parkinson's Disease and Movement Disorders Center at Northwestern University's Feinberg School of Medicine.

Simuni, at Northwestern since 2000, has worked in the field of movement disorders for almost 20 years.

She is an Ashkenazi Jew herself, which, she said in a recent telephone interview, "certainly adds an extra dimension" to her current research. She is also Todd Davis' doctor.

"We are reaching out to the Jewish community," most of whose members are of Ashkenazi background, to participate in the PPMI trial, Simuni said.

"It is important to participate for multiple reasons," she said. "Parkinson's disease is the most common neurodegenerative disease. It affects about one million people in the United States, about five million worldwide. The cause remains unknown and overall, genetic forces are very uncommon."

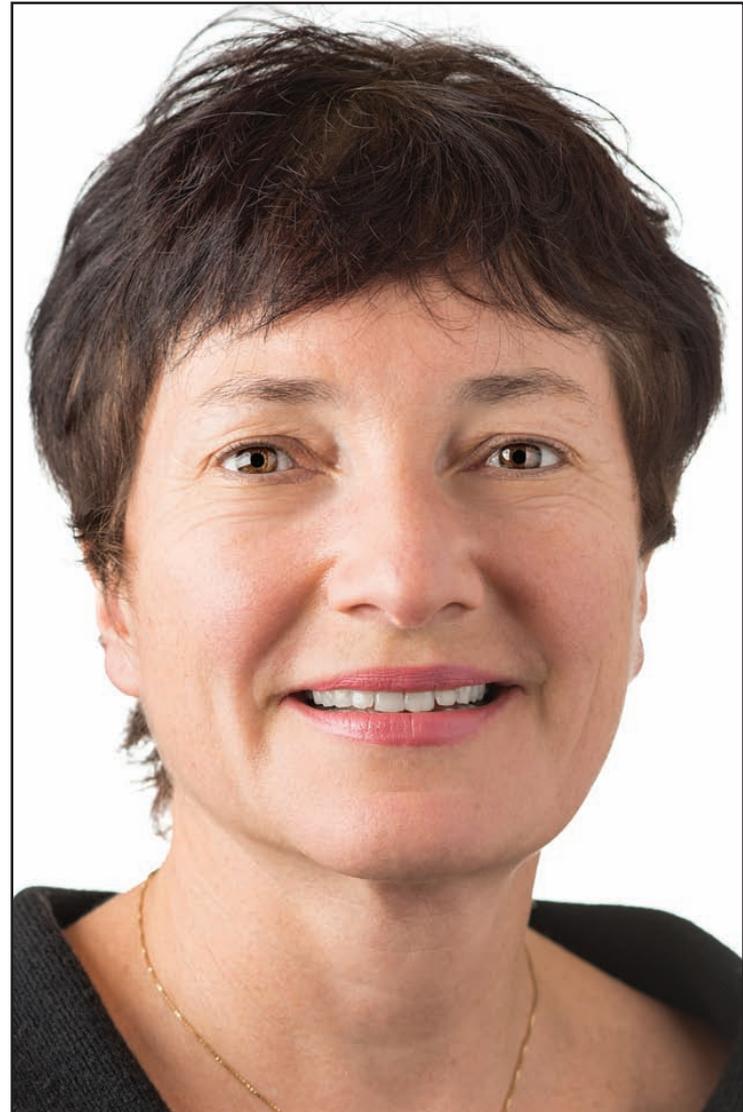
In the general population with Parkinson's, current evidence shows genetics is responsible for only about 5-10 percent.

The last decade, however, has brought an "explosion" of research into the genetics of the disease, she said. That research has shown that "in specific ethnic cohorts, the prevalence of the disease (with a genetic basis) is much much higher."

How high? Among Ashkenazi Jews who have a first-degree relative (parent, sibling, child) with the disease, the risk of carrying the LRRK2 genetic mutation may be from 20 to 30 percent, she said. In the rest of the Jewish population with no family history of PD, 10 to 12 percent carry the mutation.

Today, Simuni said, there is no way to prevent people from developing Parkinson's, although drugs exist that can alleviate symptoms to some degree.

The PPMI study, she said, is of "overriding importance in studying people with PD and



Dr. Tanya Simuni

healthy controls with the objective of developing biomarkers, objective measures of disease prevention. We can then use biomarkers to facilitate research into better therapies for the disease and then to move into prevention. Those are the goals for the future but we will never achieve them unless we make the steps we are making by looking at genetically driven subsets of PD."

The fact that the LRRK2 gene mutation appears in two different populations "is more than coincidence," Simuni said. "It all goes back to ancient, ancient common roots. These ethnic populations historically have had very little assimilation until recently with Ashkenazi Jews."

The study will have implications beyond Parkinson's disease, Simuni said. In fact it may shed light on Gaucher disease, an-

other disorder that disproportionately affects Ashkenazi Jews. Simuni said "there is a direct link" between the two diseases.

"Parkinsonian symptoms are very common in people with Gaucher, and the enzyme responsible for Gaucher also has a role in the development of Parkinson's," she said. "If you look at the Jewish population with Parkinson's disease, up to 10 percent will carry the Gaucher mutation." Carrying that mutation doesn't mean these individuals will develop Gaucher, she said.

The PPMI study, she said, "gives us the opportunity to study the disease in a small proportion of patients but the findings will be applicable to the Parkinson's disease population at large."

"There is tremendous interest in these studies in the Parkin-

son's research community and in the drug development industry," she said. "It creates a unique opportunity to develop a drug specifically for the populations with these abnormal mutations."

The Fox Foundation has 15 industry partners and sponsors for the initiative, including such major pharmaceutical companies as Abbott Laboratories, Eli Lilly, Merck and Pfizer.

The study has "ambitious goals but definitely achievable goals," Simuni said.

"We are reaching out to the Jewish community," she said. "In such a large metropolitan area as Chicago we have a unique opportunity to contribute to the study. If the Jewish population comes forward, they will benefit, their kids will benefit, their friends will benefit."

The study researchers are seeking Ashkenazi Jews who have Parkinson's in addition to those who don't have the disease but have a first degree relative who has it.

"The Michael J. Fox Foundation has put tremendous efforts and resources behind the study," she said. "They are committed to advancing the development of an ultimate treatment for Parkinson's disease by continuing the study."

Spector, the Ashkenazi Jewish woman who tested positive for the genetic mutation, found out about the PPMI study when she accompanied her husband, as she always does, on a visit to Dr. Simuni. She agreed to be part of it right away.

"I have been my husband's caregiver for almost 25 years. Anything I could do to help the cause of being able to detect (Parkinson's) earlier and treat it, I would do," she said.

Carrying the genetic variance means "there is some increased risk for developing the disease but nobody can tell how much," Spector said. "It does not mean you are going to be fated to

have Parkinson's disease. And there is nothing you can do about it."

She thinks that one of the most important goals of the study is to find a way to detect Parkinson's earlier. Individuals are often told that losing their sense of smell may be an early marker for the disease, but, Spector said, "that's pretty vague. They would like to find some more objective way of testing. They will try and take a really close look to tell what the really early symptoms might be," similar to finding that people with high glucose levels are at risk of developing diabetes.

"By the time you develop speech problems and tremors, the damage is already done. You're well into it," Spector said.

That was the case with her husband, she said. "People don't think about it, their doctors don't think about it. My husband had trouble walking and balance problems. By then the cells Parkinson's disease affects are already damaged."

Davis, who lives in the Self-help Home on Chicago's North Side, clearly demonstrates the effects of the disease but also shows how much a determined individual can overcome. He greets a visitor pleasantly from a chair, then proceeds to "warm up" his voice with a series of exercises that loosen up the muscles around his voice box to try and forestall as much as possible the speech difficulties that often go along with Parkinson's. He speaks softly but is not hard to understand.

"You learn how to watch the reaction of the person you're talking to to see if you're speaking loudly enough," he said. He points out that he occasionally bobs his head, a reaction from one of the drugs he takes.

He does other types of exercises too and said that "exercise is terribly important" to someone with Parkinson's. "You slide back if you don't keep at it," he said.

Davis participates in many activities and goes to Children's

Hospital, his former workplace, one day a week, where he supervises residents. "It keeps me occupied," he said.

He said he is not worried about his wife developing Parkinson's, even though she carries the genetic mutation, because no one else in her family has the disease.

Will there ever be a cure? Davis is optimistic.

"First they need to find out how the gene affects the body chemistry," he said. "It's not likely they will have a startling breakthrough in the next 10 years. It will take five to 10 years to test a drug for Parkinson's" even if one is developed, he said, adding that developing a new drug takes an average of 17 years before it gets to the patients who need it.

Spector said she is not so much focused on the possibility that she might get the disease as she is on her husband, who doesn't share her Ashkenazi Jewish gene pool.

"He has had the full-blown disease for almost 25 years," she said. "When you live with that and see the sad and tragic changes that have occurred in his life, I'm willing to do whatever I can to help find a better diagnosis."

Davis, she said, "works very hard, faithfully doing his exercises. He has strong muscles and is very determined to stay active. But it is a terrible, terrible disease. He was a very good pediatrician, he wrote and read all the time, his patients loved him and he had to retire so young. He was an old school doctor, always very available to parents. At Children's (Hospital) he trained several generations of pediatricians. At this retirement party some of the mothers cried."

The toll the disease takes after a number of years is evident in another resident of the Selfhelp Home, Helga Kauf-Berman, whose Parkinson's is far more advanced than his own, Davis said. (Kauf-Berman is not involved in the PPMI study.)

At age 89, she has had the disease for about 12 years and struggles with walking and movement, although her voice is clear and strong. Her husband, author and educator Louis Berman, explains that his wife was diagnosed before the disease was evident to anyone but herself.

"One side of her body felt different from the other," he said, noting that her doctor predicted that she could live a normal life for about the next five years. The couple then traveled and engaged in other activities until the disease became more burdensome, he said. Then he retired and took over such activities as shopping and meal preparation. Soon Kauf-Berman's doctor suggested that the couple move from their Wilmette home into a re-



The Michael J. Fox Foundation is launching a new phase of a study on the causes of Parkinson's and is actively seeking help from the Jewish community in Chicago.

retirement community. "This was the right place," Berman said.

He said that he often views a tape of Kauf-Berman, a Holocaust survivor, being interviewed for Steven Spielberg's oral history project. "You can see what a splendid woman she was," he said.

Even today, Berman said, "she has no trouble speaking or hearing and her memory is very good. She will correct me sometimes." Like Davis, she exercises faithfully even though it is often difficult, he said.

Berman has become active with Parkinson's organizations and often attends meetings and conventions.

Kauf-Berman, for her part, replies that she is "lousy" when asked how she feels and looks uncomfortable sitting in a chair, her body contorting as she talks to a visitor.

She said she wants to tell everyone, "I hope they never

get" Parkinson's. But her most important message is "Give money for research."

Spector, meanwhile, praises the "wonderful, caring, compassionate" Dr. Simuni and urges members of the Jewish community to come forward to be tested.

"This is a good way to play 'Jewish geography,'" she said. "Somebody who knows somebody who knows somebody - this is how we will get the word out."

Medications for Parkinson's "have come a long way, along with the recognition that physical therapy is very important," Spector said. "Nevertheless it marches on and there is really nothing you can do. Every year, every month you see the changes, you see it get worse. My husband is somebody who has done a great deal of good in the world. Life is unfair, but this seems particularly unfair."

About the study

Northwestern University and the Michael J. Fox Foundation, partners in the Parkinson's Progression Markers Initiative, are looking for people of Ashkenazi Jewish descent who either have Parkinson's disease or do not have it but are over 50 years old and are related to someone who has the disease.

Volunteers who enroll will first undergo screening to confirm their eligibility to participate. If eligible, individuals will undergo a battery of tests and assessments that include a medical history, neurological exam, physical exam, vital signs, blood testing, MRI and other tests.

After the first screening, participants will visit the center every six months for up to five years for either short or long visits and further assessments.

Participants will be paid a small amount to thank them for their time. Additional funds are available if needed to help with travel and other expenses.

The study is observational only and participants will not receive any drugs or medication.

To learn more, contact Jennifer Olson or Karen Williams at (312) 503-0755 or email pd-clinicaltrials@northwestern.edu or visit www.michaeljfox.org/PPMI/genetics.