

How I Am
Helping Fight
Parkinson's
Disease

Real people suffering
from this illness are
assisting genetic
research as it narrows
in on the disease's
underpinnings

By Devorie Kreiman



Interior (below) and exterior (right) of the Sourasky Medical Center in Tel Aviv



Dr. Roy Alcalay

Dr. Roy Alcalay is a neurologist who focuses on movement disorders, primarily Parkinson's disease. He is the head of the Movement Disorders Division at the Sourasky Medical Center in Tel Aviv, Israel. Dr. Alcalay is also on the global research team of the Parkinson's Progression Markers Initiative (PPMI), launched by the Michael J. Fox Foundation in 2010 to identify biomarkers of Parkinson's and to help researchers set up clinical trials that will hopefully enable the development of better tools to diagnose, treat and prevent this disease.

At present, the PPMI team is looking for volunteers—with and without Parkinson's—to participate in research on genetic mutations. Some mutations are more common in selective groups. For example, the LRRK2 and GBA gene mutations, which are linked to Parkinson's disease, occur more frequently in *Ashkenazi* Jews than in the general population, so PPMI is interested in recruiting *Ashkenazi* Jews, among others.

Reni Winter-Evans is a participant in this research. Here is her story.



A farm in Tippecanoe County, Indiana

I am 68 years old. My mother came from an Ashkenazic family that emigrated from Ukraine in the early 1900s. My father was Sephardic, a Marine who fought in Okinawa at the end of World War II.

When I was six months old, my father was diagnosed with paranoid schizophrenia triggered by the trauma of his experience in combat. He was hospitalized, and my parents divorced.

In the 1950s, many people who suffered from mental illness were hidden from sight and cut off from their families. I grew up with no memories of my father. As a teenager, I learned about genetic predisposition. I knew about my father's schizophrenia and how horrific it was. My mother sent me to talk to a counselor because of my fear of inheriting it from him.

My stepfather was a Holocaust survivor. He loved to take our family on long rides into the countryside and tell us stories of growing up in Czechoslovakia before the Nazis destroyed his village, his family and his youth. Growing up in the home of a survivor made me different from the other Jewish kids in school. I felt his heaviness

and suffered with him. I was determined to make things better. I became the happy child. No matter what was going on, my stepfather called me his ray of sunshine. This would impact the way I dealt with my own challenges as I grew older.

From the time I was a young girl, I dreamed of living on a small farm. After high school, I went to Israel and worked on a kibbutz, but I didn't fulfill my parents' wish that I stay there and marry a sabra.

More than 20 years ago, when I was in my 40s and working as a social worker, I began to search for my biological father. I tracked him down in the psychiatric ward of a VA hospital. I found out that my great-grandfather, David Ohana, had loved nature, spoke seven languages, and was a *sofer* and a skilled embroiderer who made covers for *sifrei Torah* out of silver and gold. I was astounded. I also loved nature, was unusually good at languages, and had also been driven to sew and quilt. Although I had always worried about inheriting schizophrenia, little did I know that I was at risk of inheriting other health woes as well.

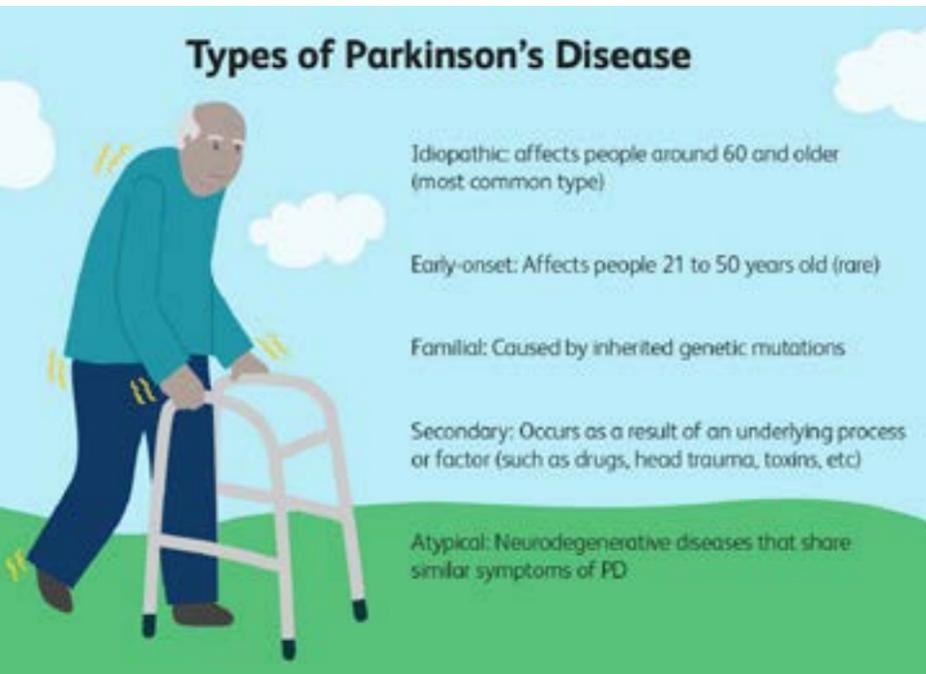
My biological father had a shuffle, gait issues and mild tremors, and his posture

was stooped. All of the signs were there. I can see them clearly in hindsight. But he was severely mentally ill, so that was front and center. We never talked about Parkinson's. I don't know if he even knew he had it.

My stepfather passed away in 2004, and my mother passed away a year later. With the money they left me, I bought a 13-acre farm in Tippecanoe County, Indiana. The land was fertile, and the water from my well was full of minerals and nutrients. I named my farm Winter Haven and grew acres of prairie grass, native plants and wildflowers.

I took a job as a germinator at the Dow AgroSciences seed laboratory to learn more about the process of germinating seeds. I was enthralled by the fact that something so tiny contained all of the genetic information necessary to bring about new life. My work involved testing genetically modified seeds to discover how long and under what conditions they would germinate.

We wore lab coats and personal protective equipment because the area was treated with insecticides. I was given goggles and gloves to protect my eyes and hands,



but I didn't cover my face or protect my lungs. This turned out to be very significant later on, when I studied the confluence of genetics and environmental factors such as toxins in pesticides and air pollutants.

During the year and a half that I worked for Dow, I noticed that my foot kept catching on the floor as I walked down the long hallways to the lab. Somehow, I couldn't lift my foot high enough to clear it. I thought, *Why am I tripping on nothing?* I didn't know that it was the start of "foot drag." I was also dropping things like crazy. When I was in motion, my brain and body didn't coordinate, and I would walk into walls. I also fell a lot and broke a rib, my nose and a wrist.

I had other symptoms as well...a slight tremor, a metallic taste in my mouth, like smoke. I lost my sense of smell, had difficulty falling asleep and staying asleep, and I started to choke on food because I couldn't coordinate my breathing and

swallowing. I became irritable, intolerant and grumpy. I had no idea what was happening to me.

In 2012, I was working on a home health-care team. One of my patients, who suffered from late-stage Parkinson's disease, had become very agitated. I suggested lavender aromatherapy. The patient's sister said, "That won't help. She can't smell anything. That's part of her Parkinson's."

At that moment, something clicked in my head. I started to put the pieces together. My "foot drag" down the halls. My inability to smell. Could I have Parkinson's disease? Working in hospice, I had seen patients with Parkinson's who were terminal. There was hardly anything we could do for them. I was so frightened.

Parkinson's disease, named for Dr. James Parkinson, who described the disease in 1817, is caused by a depletion of dopamine in the brain. Dopamine is a neurotransmitter, a chemical messenger between neurons in the brain that send sig-

nals to other neurons to coordinate the movement of muscles and regulate mood and other functions.

The symptoms of Parkinson's begin slowly and worsen over time. They include tremors, the vibrating or trembling of limbs; bradykinesia, meaning slowness of movement; shuffling, foot dragging and uneven gait; a sensation of the feet being frozen or stuck in cement; stiff muscles or a reduced range of motion; soft or slurred speech; and impaired balance and posture. As the disease progresses, many patients experience cognitive decline and emotional dysregulation.

In 2018, when I was completing my master's degree and was under a lot of stress, my symptoms worsened. I went through some of my parents' old paperwork and found my biological father's death certificate. The doctors had told me he'd died of a heart attack. I checked the certificate; in the box indicating cause of death, it said heart attack and Parkinson's disease.

My husband and I did a genetic test through 23andMe. Waiting for my results was a nail-biting experience. Finally, I got them. First, I checked for what I'd always feared; I looked up the genomic identity for schizophrenia on the NIH database, compared it to my genetic profile and discovered, to my relief, that I hadn't inherited schizophrenia from my father. Then I checked for the DNA mutations that may predispose a person to developing Parkinson's disease.

Our genes contain the instructions that tell the cells in our bodies how to make proteins, giving each cell its particular role. The proteins in each cell do all the work. They are the enzymes that break down our food, make energy to keep our cells working and maintain their shape, help move the cellular machinery around where it needs to be, and communicate among the different cells in the body. Humans are 99.9 percent genetically identical to each other. The .1 percent that's different is enough to create a wide variety of traits that make us unique, such as the color of our hair and eyes or behavioral traits.

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When children inherit a disease-causing mutation, it doesn't necessarily mean that they will develop that disease, but it does raise the likelihood, especially in combination with environmental factors.

My report showed that I had the LRRK2 mutation. I went for a brain scan, and my doctor diagnosed me with prodromal Parkinson's disease, "prodromal" meaning the initial stage of an illness before the appearance of full-blown symptoms.

For patients whose Parkinson's disease is linked to the LRRK2 mutation, there's bad news and good news. The bad news is that carriers of the mutation have the highest chance in the world—30 percent—of developing Parkinson's. The good news is that the form of the disease typical for carriers of that mutation is milder than some of the other versions. Some research also suggests that patients with the LRRK2 mutation have less cognitive decline and usu-

ally remain highly functional, especially with intervention.

It has been said that "genes load the gun, and the environment pulls the trigger." In the case of Parkinson's disease, scientists are studying both. The LRRK2 mutation is of great interest to researchers working on slowing or stopping the rising incidence of Parkinson's around the world. In recent years, I have personally experienced a wave of genetic influence far more intense than any nurture could be. Because I carry this gene mutation, I feel duty-bound to tell people how important it is to find answers.

From the very beginning, I was proactive about my own care. I signed up as a research participant in the Parkinson's Progression Markers Initiative (PPMI), conducted under the auspices of the Michael J. Fox Foundation. It's a multifaceted international effort to gather information from people—with and without Parkinson's—

to learn more about how the disease starts and changes over time in order to help scientists diagnose, treat and hopefully even prevent it. As a PPMI volunteer, I provide valuable data through clinical assessments and by sharing biological samples of blood and spinal fluid. I've joined other observational studies as well.

I understand that fear can be a formidable enemy, so I fight it by learning as much as I can about Parkinson's disease. I call those who have the LRRK2 mutation "Larkies" and those with the disease itself "Parkies." People with the LRRK2 mutation who have Parkinson's disease are "Larkie Parkies."

My doctor started me on dopamine agonists, medications that are often used as a first-line therapy in patients with Parkinson's. I discovered that exercise helped relieve many of my symptoms. I swim, dance, do cardio and "rock steady boxing," which focuses on maximizing the mental, emotional and physical potential of those with Parkinson's. I even bought myself a pair of boxing gloves imprinted with the words "Fight Parkinson's"! After reading the research on anti-inflammatory nutrition, I was inspired to go on a Mediterranean diet. And just in case I need it, I carry around a colorful trekking pole.

Last year, I had a terrifying experience that led, surprisingly, to a breakthrough. I was helping my husband in the yard when I stepped into a pile of leaves, unaware that there was a nest of hornets underneath it. I felt a strange sensation moving up my leg and the worst itching I'd ever experienced. I wanted my skin to come off. My body was covered in hives, I felt dizzy, as if I were floating, and I had trouble breathing. My husband took me to the emergency room, where I was treated for anaphylactic shock.

Because I live on a flower farm, it's critical that I build up a tolerance to stinging insects. I was therefore put on venom desensitization therapy, which means being injected with venom in very small amounts that are gradually increased. Within a day or two of the stinging attack, I noticed that

I was walking more easily and not choking on my food. I also noticed that every time I visited the allergist and had an injection of venom, I felt better overall. I wondered if there was a connection. Could bee venom be used to treat Parkinson's?

I discovered that there are actually several studies on this underway. The first trial didn't show bee venom to be effective, but researchers concluded that it didn't cause any harm, leaving open the possibility of further studies.

I credit my Parkinson's disease with making me a better social worker. Many of my patients suffer from chronic illnesses. Some Parkinson's patients remain fixated on the way things used to be, but life doesn't work that way. We can only go forward. When they despair about no longer being able to do things or give to others, I tell them, "For everything there is a season, an appointed time, and it's your time to receive help."

I call it radical acceptance. When we are faced with challenges over which we have no control, we have to figure out how to cope. We cannot argue that it isn't fair. I tell my clients, "Imagine you're holding a priceless vase and it slips out of your hands. It's about to hit the floor, where it will smash into a thousand pieces. You can't stop it; all you can do is accept that it's happening."

I accept that I have this genetic mutation, and I am committed to doing whatever I can to be part of the solution both for myself and for others. I choose to have the best possible quality of life in the context of what I cannot change. I might not be able to reverse the process, but there are interventions that can make life with Parkinson's easier.

I urge people not to ignore signs of illness, to get genetic testing and to participate in the research. You may think that ignorance is bliss, but the truth is that knowledge is power.

My message to the Ashkenazic population is this: Please pay attention. Step up and participate in the research. As Hillel said, "If I am not for myself, who will be for me? And if not now, when?"

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Please tell us a little about yourself.

PI grew up in Israel. I knew from a very young age that I was interested in the brain. When I was serving in the IDF, I took open university classes in neuroscience. I obtained my medical degree from Tel Aviv University; I did my residency at Massachusetts General Hospital and Brigham and Women's Hospital, which is affiliated with Harvard, and my movement disorders training at Columbia University.

Describe the work you do in treating patients with Parkinson's disease.

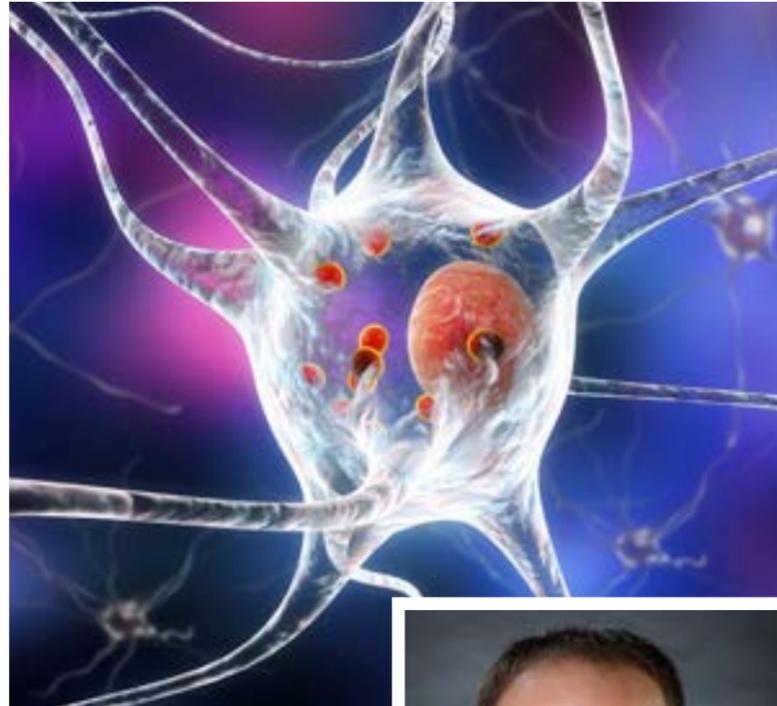
My work has two components. I'm a treating physician and a researcher.

Some patients come to me with tremors hoping that it will turn out to be something other than Parkinson's, which it sometimes is. Patients also come to me to confirm a diagnosis of Parkinson's disease. It's a difficult job because almost every day I have to deliver challenging news. When I tell patients that they have Parkinson's, I encourage them by stressing that there is hope and that we will help them manage their symptoms and improve their well-being.

I find that my patients do best when they are part of a team that includes family members, doctors, physical therapists and community members. I've seen the community step in to help in many important areas, such as setting up health portals or facilitating Zoom sessions for patients who don't have Internet access. It's an ongoing relationship.

When I worked in New York, I saw patients from Brooklyn and Monsey who were referred to me through Refuah Helpline. Many of them stop by to say hello when they come to Israel. My patients are warriors. I see how they handle hardship, and it gives me strength to stay in the fight on their behalf. I let them know that they are getting into a race with science, and we hope that science will win before their disease progresses.

I've dedicated my career to researching Parkinson's disease in order to help the next gen-



3D illustration showing neurons containing Lewy bodies small red spheres which are deposits of proteins accumulated in brain cells that cause their progressive degeneration.



A Conversation with Neurologist Dr. Roy Alcalay about Parkinson's Disease and the Ongoing Research to Treat It

eration. Right now, we help our patients by managing their symptoms in order to improve their quality of life, but through research focusing on genetics and biomarkers, we are working to slow the disease down and hopefully prevent it.

Ashkenazic Jews are more likely to carry genetic variants that increase the risk of some diseases, including Parkinson's. I'm hopeful that the research into the genetics of Parkinson's will enable us to offer patients precision drugs that are tailor-made for them.

How does the Parkinson's Progression Markers Initiative work?

In many cases, by the time patients are diagnosed with Parkinson's, they have some damage in their brains. In order to measure their progression earlier and with more accuracy, researchers need to find biomarkers—measurable characteristics in the body such as blood pressure, heart rate, scanned images or changes in blood or tissue—similar to the way heart attacks used to be diagnosed by chest pain but are now verified by levels of enzymes in the blood. Because the biomarkers for Parkinson's are not yet known, PPMI is collecting data from scans, blood and urine in an effort to identify early indicators.

Just this year we discovered a biomarker in spinal fluid that may tell us if a patient has early Parkinson's disease. We are now studying ways to detect that biomarker from nasal swabs, blood or skin samples, which are less invasive.

The PPMI study also focuses on the genetic mutations that may lead to Parkinson's—including LRRK2 and GBA—which are prominent among Ashkenazic Jews. When scientists understand how a genetic mutation causes the protein in the cell to act differently, they can target those changes and work to restore the protein's function. If we can modify the gene, we may be able to slow down or prevent Parkinson's disease.

Only some of the people who carry the



“No one is forced to participate in research, but when people choose to do so, it's a real chesed.”

mutations linked to Parkinson's actually get it. PPMI researchers are asking why, analyzing factors such as environmental toxins, other genetic variants and lifestyle. So far, nearly 1,500 people have enrolled in PPMI at 50 medical centers around the world, and another 20,000 are contributing valuable insights online.

What does a study participant have to do?

PPMI is an observational study that follows participants over time as they share important information about their health. There are no drugs or therapies tested on participants.

Most people will contribute data to PPMI online. Others may complete remote screening tests, such as using a saliva collection kit or a scratch-and-sniff test. Some will join PPMI at one of its official clinical sites. They are asked questions about their health. The more information the researchers collect, the greater their chances of finding breakthroughs.

In some cases, participants are asked to take part in further studies, such as a brain scan to measure dopamine levels, or to contribute bio fluids such as blood, urine or brain fluid through a spinal tap. There is no obligation to do so.

In order for PPMI to expand its research

and get closer to finding better treatments and prevention methods, the study needs to recruit more people. Adults 60 and older are especially needed.

Why is it important for people to get involved in research?

Millions of people suffer from Parkinson's disease. Many studies that have the potential to lead to lifesaving treatments are slowed down because they don't have enough participants to get results that are strong enough for statistical validity.

This is an opportunity to make a real difference. No one is forced to participate in research, but when people choose to do so, it's a real *chesed*. To me, the people who show up to participate who are healthy and don't have a family history of Parkinson's are *tzaddikim*.

In 2018, I had a *frum* patient, a mother of nine children who knew that she was a carrier of the GBA mutation. At the time, I was running a clinical trial at Columbia University on the genetic mutations that cause Parkinson's disease. I told her about it and explained the pros and cons of participating in the trial and taking a new medication. She wanted me to speak to her rabbi, and I did. The rabbi encouraged her to take part in the trial.

That particular trial ultimately failed, but we are not discouraged. I'm grateful to that rabbi for recognizing the importance of our work. I tell people, “You don't choose your genes. You don't choose to get Parkinson's. But you do choose what you do.” That brave woman chose to join the fight.

Who is a good candidate for the PPMI study?

People in the early stages of Parkinson's disease, meaning within two years of diagnosis; relatives of Parkinson's patients; people who know they carry a genetic mutation linked to Parkinson's; and people who show some early symptoms, particularly a reduced ability to smell unrelated to COVID or those who act out their dreams while asleep, a phenomenon known as REM sleep



“Studies are finding ways to measure slight changes in balance and gait before they develop into full-blown symptoms.”

behavior disorder. When we dream, there's a mechanism in the brain that shuts down the muscles to prevent us from acting out what we are dreaming. When that part of the brain malfunctions and the patient is active during sleep—falling out of bed, kicking or talking—it may be an early risk indicator for Parkinson's. People with no symptoms or risk factors are important in the study as well because they serve as control volunteers.

Think about it this way. Every drug that's available in every area of medicine reached the market only because people—with and without a risk or diagnosis—volunteered to participate in a study. Every single person counts.

How is participants' privacy protected?

There are strict safety protocols in place. All information is kept in password-protected and encrypted databases. The answers people submit are compiled with data from other participants, and all names and identifying information are removed. Scientists who access the data must go through an application process and sign an agreement to protect participants' privacy. The information is not made available to anyone outside the research community.

Is there a 100 percent guarantee that there won't be a data breach? PPMI does all it can to protect the privacy of participants, but as with anything shared online, there is no guarantee. That said, the hope is that the chance to be part of something great will be worth the risk.

It's important to know that if there are any questions that make people uncomfortable, they can skip those. And they can withdraw from the study at any point.

What treatments are currently available for people with Parkinson's disease?

There is no known cure at this time. However, there are ways to improve patients' quality of life by addressing their symptoms.

In people with Parkinson's, the brain

cannot produce sufficient levels of dopamine. Drugs such as levodopa—a dopamine precursor that the body can convert into usable dopamine—are often combined with carbidopa—which blocks dopamine degradation in the body outside of the brain, ensuring that the levodopa actually reaches the brain.

There are a handful of similar drugs available and more that are still in clinical trials. Unfortunately, these medications may cause long-term adverse side effects. Drug makers are currently working on ways to optimize dopamine delivery to the brain with more immediate effect and fewer adverse events—for example, by delivering levodopa through an inhaler or an oral strip, or under the skin.

Techniques such as surgery, deep-brain stimulation and electrodes are also being used to treat some patients, with varied levels of effectiveness.

There are many innovative therapies in the works to ease some of the symptoms of Parkinson's disease. For patients who suffer from an uneven gait, companies are developing drugs to improve balance and the ability to pay attention in order to avoid falls. For people with Parkinson's, walking is diffi-

cult because they are unable to plan where they are going and take a step at the same time. Scientists are developing a laser that shines spots on the ground. It acts as a circuit reset and takes away the need to focus while walking; all patients have to do is step into the spots that are in front of them.

What other research is currently in the works?

Clinical trials are underway to develop drugs that target the changes in the protein of the cells linked to the mutations. Three genes are being studied extensively—LRRK2, GBA and SNCA (alpha-synuclein). These trials are in various phases of testing, including early safety testing to ensure that no harm will be caused, early efficacy testing to see if the drug has a benefit, and larger-scale trials in which groups of people with and without the mutation and/or the disease are monitored as they take the medication or a placebo.

The pace of research into Parkinson's disease has picked up in the last decade because the open-science concept popularized by studies such as PPMI encourages scientists to collaborate rather than compete in the race for a cure. In addition, advances in molecular and genetic technology and greater computing power allow researchers to collect and analyze data more quickly and efficiently.

Studies are underway to find ways to measure slight changes in balance and gait before they develop into full-blown symptoms. There is also a lot of information gathering and analysis on how environmental factors such as toxins combine with ethnicity, age, diet, lifestyle choices and, of course, genetics.

Any final words for our readers?

Parkinson's disease is degenerative. It's a daily reminder to be thankful for what we have. ●

For more information or to sign up to participate in PPMI, go to ppmi-info.org.

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