Parkinson's Update

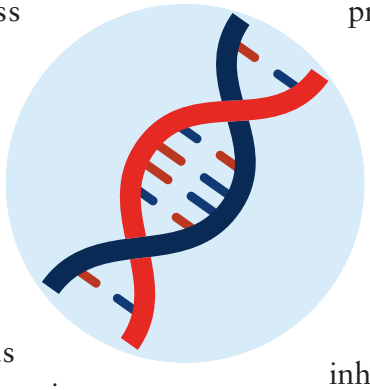
Parkinson's Disease and Movement Disorders Center
Feinberg School of Medicine
Northwestern University

Fall 2015 Vol. 21

The Genetics of Parkinson's Disease

By Lisa Kinsley and Danny Bega

Descriptions of families that pass Parkinson's disease from one generation to the next have led to evolving theories on PD's cause. For much of the 20th century, Parkinson's disease was regarded as a neurodegenerative disorder with little or no genetic cause. In contrast to people with other, rarer movement disorders such as Huntington's disease, most PD patients seen in modern movement disorder clinics do not report a family history of disease. Nevertheless, it is now thought that PD has multifactorial causes. Acquired genetic changes, aging, and behavioral and environmental factors, such as chemical exposures or serious head trauma, can trigger a cascade of cellular events in a person born with a genetic predisposition to develop symptoms, pushing the person over the threshold. For first-degree relatives of people with PD, the lifetime risk for developing PD is about 3 to 7 percent.



For a small percentage of people—around 5 percent—there is a more direct kind of genetic inheritance. For them and their families, a change in one of several known genes causes PD. Genetic information within each of the body's millions of cells instructs the cell to be able to grow and function normally. When the code of a gene changes, or mutates, the proteins created by mutated genes will be different from those created by functional, nonmutated genes. Depending on the type and severity of the mutation, the changed protein can cause problems in the cells and lead to symptoms of diseases. Mutation in one of the many genes involved in brain cell function can produce symptoms of neurodegenerative disorders, including PD.

Most genes are present as two copies, one inherited from the mother and one from the father. The most common type of inheritance for genetic PD is known as autosomal dominant, meaning it takes only one gene of the pair carrying the mutation to cause symptoms. In other words, every child of a parent with the disorder has a 50 percent chance of inheriting the gene mutation that causes it.

Mutations in a gene called LRRK2—which appear to be more likely in people of Ashkenazi Jewish or Northern African ancestry—are the most common cause of autosomal-dominant PD, although not everyone who has a mutation in LRRK2 will go on to develop PD. The age of onset for patients who do averages about 58 years, but it varies greatly. The clinical symptoms are the same as those in people with nongenetic PD.

A gene called SNCA is another cause of autosomal-dominant genetic PD. It creates a protein called alpha-synuclein that plays a central role in PD and possibly other neurodegenerative disorders. Lewy bodies, the brain finding in patients with PD, contain the abnormal alpha-synuclein protein from mutated SNCA genes. The clinical symptoms are the same as

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The Genetics of Parkinson's Disease

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in people with nongenetic PD, but the average age of onset is younger—around 46 years.

Other inheritance patterns have been reported as well. Parkinson's disease can have autosomal-recessive inheritance, meaning that both copies of the PD gene need to have mutations for a person to be affected. This type of PD is rarer. Patients share a similar clinical phenotype, characterized by early onset, slow disease progression, and typically mild nonmotor symptoms. X-linked inheritance has been reported among a very small group of families and is not typically seen.

Because such a small number of patients with PD will have a mutation in a PD gene, genetic testing is not part of the routine diagnostic process. For most people with PD, therefore, the specific genetic and environmental triggers cannot be identified or proven. Depending on a patient's family history, genetic testing may or may not be ordered by the neurologist. The Northwestern Parkinson's Disease and Movement Disorders Center works with a genetic counselor who can gather a family history and discuss the genetic testing process with appropriate patients.

Genetic testing can provide not only information for the patient about the cause of the disease but also predictive information for family members interested in finding out their risk for developing PD. Northwestern's PDMDC has begun a dedicated genetics clinic and a biorepository, an effort spearheaded by Dimitri Krainc, professor and chair of the Department of Neurology and director of the Center for Rare Neurological Diseases. In addition to providing genetic counseling and testing, the clinic and the biorepository aim to obtain samples of genetic material from patients (i.e., blood, skin cells, and in some cases spinal fluid) to better understand the mechanisms behind PD and other movement disorders. This information may be highly valuable, particularly when matched with clinical data as patients are followed over time. Some samples might be used to develop patient-derived stem cell models of PD that might provide insights into the disease's pathobiology. Regardless of a person's gene status, understanding the genetics of PD and the dysfunctional proteins involved will allow researchers to better understand the pathophysiology of the disease, including the potential targets for future therapies that could be applied to the PD community at large.

Lisa Kinsley, MS, CGC, is a board-certified genetic counselor at the Feinberg School of Medicine.

Danny Bega, MD, is a neurologist and assistant professor of neurology at the Feinberg School of Medicine.

Movement Disorders Clinical Trials

Enroll-HD The goal of the open-ended Enroll-HD study is to build a large global database of longitudinal clinical information and biospecimens for future studies of Huntington's disease. It is recruiting patients with HD, their family members, and controls for annual follow-up. *Funded by CHDI Foundation.*

INTREPID (**implantable neurostimulator for the treatment of Parkinson's disease**) The objective is to evaluate the safety and effectiveness of bilateral stimulation of the subthalamic nucleus as an adjunctive therapy for improving the number of waking hours per day with good symptom control and no troublesome dyskinesia. Subjects are adults with advanced, levodopa-responsive bilateral PD that is not adequately controlled with medication. Requires 14 clinic visits and one phone call over 5½ years. *Funded by Boston Scientific Corporation.*

Levodopa Inhalation Powder This multicenter study is evaluating inhaled CVT-301 for the treatment of PD patients experiencing up to five off episodes of motor fluctuations a day. Participants are between 30 and 80 years old. Requires eight visits over 12 weeks.

Movement Disorders Center Biorepository The objective is to create a repository of DNA, plasma, iPS-derived-cell lines, and clinical information from patients, familial controls, and healthy control subjects for future research. Subjects were diagnosed with a movement disorder at age 18 or older.

Oral Istradefylline The objective is to establish the efficacy of 20 and 40 milligrams of istradefylline a day for reducing the off time in patients with moderate to severe PD who are on levodopa/carbidopa therapy and have motor fluctuations and dyskinesia. Requires seven clinic visits and one telephone follow-up over 12 weeks. *Funded by Kyowa Pharmaceutical.*

PPMI Study The objective is to identify clinical, imaging, and biologic markers of PD progression for use in clinical trials of disease-modifying therapies. The five-year study is recruiting PD subjects who do not require therapy for at least six months as well as non-PD subjects. *Funded by the Michael J. Fox Foundation.*

Steady PDIII The objective is to establish the efficacy of isradipine to slow progression of PD. The study is recruiting early PD patients who do not require dopaminergic therapy (levodopa, dopamine agonist, or MAO-B inhibitors) or PD symptomatic therapy for at least three months. The study requires 12 visits over 36 months. *Funded by the National Institute of Neurological Disorders and Stroke.*

Wilson's Disease The objective is to evaluate the efficacy and safety of WTX101 administered with a proton pump inhibitor for 24 weeks. Subjects are newly diagnosed Wilson's disease patients older than age 18 with above-normal nonceruloplasmin-bound copper levels. Requires 13 visits over eight months. *Funded by Wilson Therapeutics.*

For more information call **312-503-0755** or email **pdclinicaltrials@northwestern.edu**.

For more information about Parkinson's disease research at Northwestern, visit our website at **www.parkinsons.northwestern.edu/clinical_trials.html.**

In a Patient's Words: Benefits of Movement Therapy

By Beverly Fotiadis

I have been a participant in the Movement Therapy for Parkinson's and Other Neurological Disorders class at the Mayfair Recreation Center in Westchester, Illinois, for three sessions.

The chair, ballet barre, and across-the-floor work push me to continue difficult tasks when rigidity sets in and my physical strength weakens. The straight-spine ballet position is useful to correct my posture when my body tends to lean forward.

The instructor's "up on the toes and down" demonstrations help me to reach items in high places; "clear the table" encourages me to use long arm strokes when completing tasks (I had been using short movements).

Ballet plié exercises save me from rigidity problems such as back pain, especially when I need to pick up items from the floor. The pliés also strengthen my feet for better gait and balance.

The music added to exercise movements is very enjoyable, especially when doing across-the-floor routines. Music is therapeutic and lifts my spirit.

As my Parkinson's symptoms progress, the movement exercises I'm learning are most helpful for completing my everyday activities.

For class information, go to www.wpdparks.org or call 708-562-6410, ext. 311.

Northwestern Medicine's Parkinson's Disease and Movement Disorders Center

National Parkinson Foundation Center of Excellence

ANNUAL PATIENT AND FAMILY SYMPOSIUM

"Keystone Symposia on Parkinson's Disease"

Saturday, October 10 • 8 a.m.–12:30 p.m.
Conference Room A, 251 East Huron Street, Chicago

8 a.m.	***REGISTRATION AND CONTINENTAL BREAKFAST***
9 a.m.	***WELCOME***
9:05 a.m.	***KEYNOTE ADDRESS: "Psychiatric and Cognitive Issues of PD"*** Daniel Weintraub, MD, associate professor of psychiatry and neurology, Perelman School of Medicine, University of Pennsylvania
9:30 a.m.	***NEW TREATMENT PIPELINE*** Tanya Simuni, MD, medical director, Northwestern Parkinson's Disease and Movement Disorders Center, and Arthur C. Nielsen Professor of Neurology, Feinberg School of Medicine
10 a.m.	***PRESENTATION: "Nonmotor Symptons of Parkinson's Disease"*** Danny Bega, MD, movement disorders neurologist, Northwestern Parkinson's Disease and Movement Disorders Center, and assistant professor of neurology, Feinberg School of Medicine
10:30 a.m.	***BREAK***
10:45 a.m.	***EXERCISE AND PD*** Daniel M. Corcos, PhD, professor, Department of Physical Therapy and Human Movement Sciences, Feinberg School of Medicine
11:15 a.m.	***PRACTICAL TIPS FOR SPEECH AND SWALLOWING*** Kristen A. Larsen, MA, CCC-SLP
11:40 a.m.	***PHYSICIAN PANEL: QUESTIONS AND ANSWERS***
Noon	***BREAKOUT SESSIONS*** "Benefits of OT and PT" "Psychiatric Issues in PD" "Comprehensive Exercise Program" (Eric Johnson) "Tai Chi" (Anna York)

To register, please call Northwestern Medicine's Health Resources and Physician Referral Service at 312-926-8400.

"I Walk in Honor of My Dad"

By Amanda Baittie

Moving Day Chicago
will take place in Lincoln Park
on Sunday, October 18.

For more information
or to start a team, visit
www.movingdaychicago.org.

"I have been diagnosed with Parkinson's disease," my father said, with tears streaming down his face. "I don't have too much information on the subject, but I want you all to know that I am okay and I am going to be fine." We all held hands, cried, and hugged until he announced, "Okay, so who wants pizza?" From that moment I knew everything was going to be okay. Dad was remaining positive, so I needed to as well.

It was December 2012. I was 22 and home from college on winter break when my father announced that he had early-onset PD. He was 52 and in relatively good shape, so needless to say, the news came as a shock. Initially, the emotions I felt were out of control—I was sad, frightened, angry, and, most of all, confused. I was not familiar with PD—Michael J. Fox's diagnosis was the extent of my knowledge. I knew that he, too, was diagnosed at a young age. But his noticeable symptoms were tremors, and my dad didn't have a tremor. This must be a false positive, I thought as denial began. Denial, I have since learned, is very common among families and caregivers of those with Parkinson's. We don't want to believe something so degenerative and incurable can be attacking our loved one.

I was angry for a long time—angry that this was happening to my family, angry that my dad had to go through this, and mostly angry that I had no control over it. I found solace in research. I realized there was nothing I could do to reverse the diagnosis, so I began researching as something I could do to help. I could be informed, support my dad, and maybe help a community of others. Through my research I came across the National Parkinson Foundation. I read all the information it provided and felt confident in my base of knowledge. A few months later, we received a piece of mail from NPF about its annual Moving Day walk. I held it up to my dad and casually said, "Hey, this looks like fun! We should make a team!" That simple statement was a tiny ripple that caused a wave.

My father and I organized the Martini Shakers team and set a goal to raise $1,000. By the day of the 2013 walk, we had raised more than $13,000 for NPF. We were shocked at the generosity of our family, friends, and community and, more importantly, were overjoyed that we could bring light to the community of people living with PD. Last year, the Martini Shakers raised another $18,700 for NPF and enlisted

the support of an honorary captain from each of the 50 states and five countries.

My father, Robert Baittie, published a memoir, *Tremors in the Universe*, this year. It documents his journey with Parkinson's and spirituality—but most of all it reiterates our cause: to bring awareness to the PD community and continue to provide positive support and comic relief to both patients and caregivers. Each year at Moving Day I walk in honor of my dad, and I continue to fundraise and provide advocacy throughout the remainder of the year because I find it important to inform others. It is through knowledge and support that we can make great changes, and I am positive a great change is in store for those with Parkinson's disease.

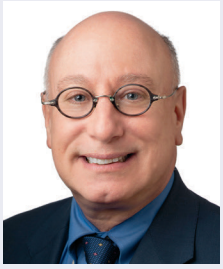
Amanda Baittie is an early childhood development teacher at the Hawthorn School in Vernon Hills, Illinois.

Using Improvisation to Cope with PD

Northwestern Medicine Parkinson's Disease and Movement Disorders Center is collaborating with the Second City improv comedy group on a research project to evaluate a community improvisation theater program for people with all stages of Parkinson's disease. Funded by the National Parkinson Foundation, the study will develop the program and assess its effects on both motor and nonmotor measures of PD severity, with the goal of improving the quality of life of patients and caregivers.

In other studies, artistic expression that involves improvisation has been shown to cultivate focus, improve communication, reduce stress, and promote feelings of acceptance, compassion, and well-being. It is hoped that the new study will demonstrate that an improvisation program will be well attended and enjoyable, can improve communication skills and quality of life, and can reduce stigma and anxiety in people of varying ages and disease severity.

For more information, call Pam Palmentera at 312-503-4397.

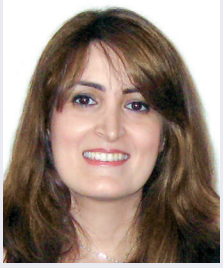


Michael Schrift

Michael J. Schrift, DO, MA, is an associate professor and geriatric psychiatry division director in the Department of Psychiatry and Behavioral Sciences at the Feinberg School of Medicine. He also directs the Geriatric Psychiatry Fellowship Training Program. He previously was the director of the University of Illinois at Chicago's neuropsychiatry/behavioral neurology program and codirector of the neuropsychiatry/behavioral fellowship training program. Schrift is board certified by the American Board of Psychiatry and Neurology in psychiatry, geriatric psychiatry, and brain injury medicine and by the United Council for Neurologic Subspecialties in behavioral neurology and neuropsychiatry.

Schrift completed his medical training at the University of Medicine and Dentistry of New Jersey–School of Osteopathic Medicine. He did his psychiatry residency at the Chicago Medical School, where he also had fellowship training in neuropsychiatry and behavioral neurology. He has a master's degree in bioethics from the Medical College of Wisconsin, where he taught neuroethics.

Schrift is a member of the American Neuropsychiatric Association, International Neuropsychiatric Association, American Society for Bioethics and Humanities, and International Neuroethics Society. His clinical and research interests are in the neuropsychiatric manifestations and complications of neurologic diseases, including neuropsychiatric movement disorders, neurodegenerative disorders, epilepsy, and traumatic brain injury.



Yasaman Kianirad

Yasaman Kianirad, MD, has started a movement disorder fellowship at the Northwestern Parkinson's Center. She completed a neurology residency at the Feinberg School of Medicine this year. She is interested in PD and hyperkinetic movement disorders.

PWR! Exercises Target PD Symptoms

By Maggie Morrissy

It is known that exercise has the potential to trigger mechanisms that may slow the progression of Parkinson's disease. As more information becomes available, what is the best exercise to ignite these mechanisms?

Becky Farley, PhD, MS PT, has used research-based principles to create a comprehensive exercise program to maximize neuroplasticity. In Parkinson Wellness Recovery: Exercise4BrainChange, more commonly known as PWR!, patients perform functional exercises that transfer to everyday activities and tasks. Created with progression in mind as well, the program allows PWR!-certified professionals to continually challenge patients to do more and create adaptations throughout their lifetimes.

"PWR! is my attempt to integrate all the essential neuroplasticity-principled components into a comprehensive exercise plan that is not limited to a strict protocol and that is to be delivered by a certified therapist or exercise professional for a discrete period of time," Farley said.

Farley created PWR! around four key concepts that are integral

to any exercise program for a person with PD:

- High-intensity exercise: You must push yourself beyond what you perceive as your limit.
- High cognitive engagement: You must incorporate cognitive challenges during exercise to continually advance your abilities.
- High attentional focus: Don't just "go through the motions"; be sure to take your awareness to your movements and be conscious of the exercises you perform.
- High emotional engagement: Find an exercise style or exercises that are meaningful to you.

These four key concepts can be used to target specific PD symptoms, such as rigidity, bradykinesia, incoordination, and automaticity. PWR! has four basic moves to target these symptoms and help improve day-to-day activities. The moves can be done lying on the floor, seated, or standing. Each position can help with different aspects of daily life, from getting out of bed to walking down a busy street while carrying on a conversation.

For more information about PWR!, check out the Rehabilitation Institute of Chicago's Fitness Center course offerings at www.ricsports.org or Farley's book *PWR!Moves: Make FUNction Exercise!*

Maggie Morrissy, MSEd, is lead exercise physiologist at the Rehabilitation Institute of Chicago's Fitness Center.

Parkinson's Disease Research Study

Do you have Parkinson's disease?

Do you currently take levodopa?

Are you experiencing dyskinesia (involuntary twisting and turning) that you find troublesome?

If you answered yes to all of these questions, you may be eligible to participate in a clinical research study to look at the safety and effectiveness of an investigational medication, ADS-5102 (amantadine HCl) extended-release capsules, for troublesome dyskinesia in subjects with Parkinson's disease.

If you qualify, your participation will last up to 16 weeks and include nine office visits. At the end of this study you may have the option to transition to a one-year open-label study of the same drug, ADS-5102 (amantadine HCl) extended-release capsules, lasting 55 weeks and including nine office visits.

Study drug, study-related exams and evaluations, and all study tests will be provided at no charge. Eligible participants may also be reimbursed for travel expenses.

For more information

Contact Joy Geallis at 312-503-4121 or Joy.Geallis@northwestern.edu
Northwestern Medical Group Department of Neurology
675 North St. Clair Street, Galter Pavilion 20-100, Chicago, Illinois 60611

Diabetic Drug Not Promising for PD

A substantial number of effective therapies to treat symptoms of Parkinson's disease are available today, but no interventions have been proven to slow progression of disability despite multiple clinical trials.

The Neuroprotection Exploratory Trials of Parkinson's Disease program, created by the National Institute for Neurological Disorders and Stroke in 2001, evaluates antiprogression therapies. Recent preclinical and early clinical evidence raised hope that pioglitazone (Actos®), an FDA-approved treatment for type II diabetes, might have neuroprotective effects in early PD and other neurodegenerative diseases. A study called FS ZONE enrolled 216 participants with early PD at 44 NET-PD sites. The study tested two doses of pioglitazone compared with a placebo for 44 weeks. Unfortunately, the results, recently published in *Lancet Neurology,* did not demonstrate promise for pioglitazone's slowing progression of PD as measured by the most commonly used PD clinical scales.

The study eliminated pioglitazone from the agents to be tested in costly and lengthy Phase 3 studies. The results do not exclude the possibility that other drugs in its class might be effective, and they are being studied.

PARTNERING WITH **NPF**

The Northwestern Medicine Parkinson's Disease and Movement Disorders Center, recognized by the National Parkinson Foundation as a Center of Excellence, collaborates with the foundation on events such as conferences for caregivers and the annual Moving Day Chicago fundraising event.

The PDMDC uses support from NPF to sponsor patient/caregiver symposia and to offer support groups and classes for Parkinson's patients in communities with limited clinical and educational services. In turn, Northwestern assists the foundation in implementing NPF programs in Illinois.

Founded in 1957 and headquartered in Miami, NPF is a premier international organization funding research and providing support services, education, outreach, and advocacy for persons with PD and their loved ones. Its Centers of Excellence must provide the highest quality in patient care, implementation of best practices, leadership in developing targeted research to extend knowledge of PD, and innovative models of education, services, and outreach.

Northwestern and NPF work together to deliver high-quality patient care, make a difference, and form a united front against Parkinson's.

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Please contact us to be added to our mail or email lists or to update your address. We also welcome your comments and letters.

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Calendar

PD SUPPORT GROUP
First Tuesday of the month, 10:30 a.m.–2 p.m.
Northwestern Memorial Hospital
251 East Huron Street, Feinberg Pavilion, third floor, room A

ART AND YOGA THERAPY
Second, third, and fourth Tuesdays of the month, 1–3 p.m.
Northwestern Prentice Women's Hospital
250 East Superior Street, room Q

HUNTINGTON'S DISEASE PATIENT AND FAMILY SYMPOSIUM
September 26, 8:30–11:30 a.m.
Northwestern Memorial Hospital
251 East Huron Street, Feinberg Pavilion, third floor, room A

ANNUAL PATIENT AND FAMILY SYMPOSIUM
October 10, 8 a.m.–12:30 p.m.
Northwestern Memorial Hospital
251 East Huron Street, Feinberg Pavilion, third floor, room A

NPF MOVING DAY CHICAGO
October 18, 9 a.m.–12:30 p.m.
Lincoln Park South Fields