Spring 2017

Parkinson's Disease Foundation
A division of the Parkinson's Foundation

News & Review

Genetics and Parkinson's Disease: What's New?

People often ask, is Parkinson's disease (PD) genetic? If one of my parents has Parkinson's, am I more at risk? In rare cases, the answer is black-and-white: a specific inherited genetic change, or mutation, causes Parkinson's directly. But for most people, genetics plays a more complex role, influencing their risk for Parkinson's but not directly causing the disease.

In the past decade or so, genetics has become one of the most exciting areas of Parkinson's research, leading to a startling realization: most cases of Parkinson's likely have a genetic component. And today, that grey area — the continuum of risk for Parkinson's — is coming into sharper focus.

The Parkinson's Disease Foundation (PDF), a division of the Parkinson's Foundation, has invested heavily in genetics research, through our fellowship and career development awards to individuals, and grants to teams at our Research Centers.

The genetic discoveries made by our teams are leading to fundamental insights into the causes of Parkinson's and ideas for how to better treat the disease. The reasoning goes like this: if we understand which genes are linked to PD, we can find ways to change their activity. For example, if a gene contributes to PD by being overactive (e.g., encoding for an overactive enzyme), a drug that shuts it down might help PD, even in those without the gene mutation. Additionally, long-term studies of genes, some of which we have supported, are influencing the design of clinical trials and helping us to understand why different people experience the disease differently.

This research, in turn, paves the way to personalized therapies. Here are some highlights.

Genetics Upends Our View of Parkinson's

Today, scientists agree that genetic and environmental factors both play a role in causing Parkinson's. However, as recently as the 1990s, few scientists suspected a role for genes. One who did was Roger Duvoisin, M.D., the first research >> Read more on page 6

IN THIS ISSUE

Science News

New Support for Therapy that Reduces "Off" Time

The experimental drug opicapone significantly reduces the "off" time for people with Parkinson's disease (PD), according to the results of a phase III clinical trial published in the December 27, 2016, online edition of *JAMA Neurology*. "Off" time is common among people with Parkinson's who have been taking levodopa, the gold standard medication for PD movement symptoms, for several years. Over time, the drug's effects wear off in between doses. Drugs called COMT inhibitors can extend levodopa's benefits, but >> Read more on page 8

Molecular "Door" May Allow Toxins to Harm Brain Cells in Parkinson's

Toxic protein clumps (alpha-synuclein) enter brain cells in Parkinson's disease (PD) by unlocking a molecular "door" called LAG3, according to a study published in the September 30, 2016, edition of *Science*. The research finds that preventing alpha-synuclein from entering through this door could slow or prevent PD-like symptoms in mice, suggesting new strategies for therapies. Researchers led by Ted M. Dawson, M.D., Ph.D., at Johns Hopkins University, investigated how the protein clumps get inside of healthy dopamine >> Read more on page 8

Letter from Leadership

Dear Friends and Supporters:

I am honored to introduce myself as the Chief Executive Officer (CEO) of the Parkinson's Foundation, an organization with a rich history of serving the community.

"We are committed to accelerating the science and care for Parkinson's."
John L. Lehr

As readers may know, last year, our two legacy organizations, the National Parkinson Foundation (NPF) and the Parkinson's Disease Foundation (PDF), merged to form the Parkinson's Foundation. In January of this year, the Board of Directors named me as the new CEO. Thanks to those of you who have already extended such a warm welcome.

Our team at the Parkinson's Foundation is eager to work on your behalf to advance our mission and better meet the needs of the community. We will continue to invest in the scientific research to end Parkinson's disease and to improve the lives of people with Parkinson's and their families, through improved treatments, support and care.

As we look ahead, there are already exciting events on the horizon and many ways for you to get involved during April, Parkinson's Awareness Month, and beyond. This June, for example, the Parkinson's Foundation is bringing together the best scientific minds in the field for a cutting-edge event, *World Without Parkinson's: A Look Into the Future*, to mark the 200th anniversary of the publication of James Parkinson's "An Essay on the Shaking Palsy." We are also bringing together the Parkinson's community at several spring Moving Day® walks across the US, where we hope you will join us in raising awareness and funds for research (see more on page 11).

Lastly, we are looking forward to our gala on Wednesday, May 31st in New York City, at which we will honor Robin Elliott, longtime leader of PDF, now CEO Emeritus of the PDF division, for his two decades of service to the Parkinson's community.

At the Foundation, we know that this is a pivotal time, one in which the needs of the Parkinson's community and the potential of science are greater than ever. That's why we are committed to accelerating the science and care for Parkinson's on behalf of the millions of people across the globe living with the disease.

We look forward to working with you to ensure that people with Parkinson's and their families have the tools they need to live well with the disease today, and to end the disease once and for all. We are stronger together.

Yours in the fight,

John L. Lehr
Chief Executive Officer
Parkinson's Foundation

In Our Inbox

Community Welcomes John L. Lehr as CEO of Parkinson's Foundation

As a second generation person with Parkinson's, Vice Chair of the People with Parkinson's Advisory Council, PDF Research Advocate, PDF Champion, writer, presenter, PDF grant reviewer and participant of 10 research studies, welcome Mr. Lehr! We look forward to working with you in any way that we can.
A.C. Woolnough, Vice Chair, People with Parkinson's Advisory Council, via email

Welcome Mr. Lehr. I wish you a wonderful journey ahead!
Robin Katsaros, PDF Research Advocate, via Facebook

Congratulations Mr. Lehr. It's good to know that people like you are leading the charge to help people like me who live with Parkinson's.
Robert Strathmann, via email

Viewers React to Online Seminar: Pain in PD

This webinar was an excellent overview of all aspects of pain as it relates to Parkinson's.
Anonymous, via survey

Dr. Fleisher was exceptional in terms of her knowledge, presentation style and her empathy for people with Parkinson's. She is one of the very best speakers on Parkinson's disease that I have ever heard.
Anonymous, via survey

This seminar was amazingly informative given that it was only an hour. It was well presented for both people with Parkinson's and caregivers.
Anonymous, via survey

[Note from the editor: View this webinar and past ones online at www.pdf.org/parkinsononline.]

Share comments and suggestions with the Parkinson's Disease Foundation at 1359 Broadway, Suite 1509, New York, NY 10018, info@pdf.org or (800) 457-6676.

www.pdf.org

Informing the Next Generation of Parkinson's Therapies

How can we improve the next generation of therapies for Parkinson's disease (PD)? Alexandra Nelson, M.D., Ph.D., of the University of California, San Francisco, was recently awarded a Stanley Fahn Junior Faculty Award from the Parkinson's Disease Foundation (PDF), a division of the Parkinson's Foundation, to find out. Using a groundbreaking technology called optogenetics and the $300,000 multi-year award from PDF, Dr. Nelson is advancing what we know about the brain's cells and circuits and how they are affected by the gold standard PD drug, levodopa. Here, she shares her early findings.

Q. Can you summarize your PDF-funded research?

A: Our goal is to understand how levodopa changes brain activity, so we can improve current therapies and find better ones. Early in my training, I was amazed to see the benefits of levodopa in people with early stage PD. However, in the later stages of PD, levodopa both alleviates symptoms *and* triggers dyskinesia (uncontrolled twisting movements). Why would the same drug produce positive and negative effects? My team is using a technique called optogenetics and a mouse model of Parkinson's to find out. We're observing up-close how levodopa affects cells and circuits in the mouse brain.

"Our hope is that this knowledge will lead to targeted treatments for Parkinson's."

Alexandra Nelson, M.D., Ph.D.

Q. What is optogenetics?

A: Optogenetics is a groundbreaking technology that uses light to turn specific brain cells "on" or "off" and observe the effects. The technique is helping us to understand how different types of brain cells work. For example, in the striatum — a key movement region of the brain affected by PD — there are two main types of cells. We think that they control the body's movement in different ways, but older techniques didn't allow us to differentiate what each cell type was doing. For example, is one helping in PD, and the other causing problems? Optogenetics enables us to monitor both cell types in mice before and after levodopa treatment and compare the responses. The findings will help us to understand the cell types, and whether they are involved in the drug's benefits or side effects.

Q. Can you share early findings? How might the results impact the community?

A: Yes, our experiments are already yielding exciting results! Researchers have long suspected that Parkinson's leads to an imbalance in activity between the two cell types in the striatum and have thought that levodopa may work by re-balancing them. However, this has never been proven in living animals and has remained controversial. Now, our research has proven both ideas — confirming that an imbalance exists between the two cell types and that levodopa can restore the balance. But our studies also showed that during dyskinesia, levodopa may instead *unbalance* cell activity in a specific population of cells. Further research is needed to understand this observation. But it's possible that targeting this population of cells, and preventing the imbalance, might lead to better therapies. Overall, our hope is that this knowledge will lead to targeted treatments for Parkinson's that can alleviate symptoms without triggering dyskinesia.

Q. Is there anything else you'd like to share?

A: I am inspired by the people with Parkinson's disease and families with whom I work, especially their grace and ability to cope with this disease. I take this inspiration back to the lab, which gives my students and me the urgency and motivation to continue our work. I would add that PDF support, which is a risk given I am an early-career investigator, has been absolutely critical to kickstarting our ideas.

Pain in Parkinson's Disease

By Jori E. Fleisher, M.D., M.S.C.E.

If you live with Parkinson's disease (PD) and experience pain, you are not alone. Chronic pain is twice as common among people with PD as it is in people who don't live with PD. In fact, more than 80 percent of people with PD report experiencing pain and many say it's their most troubling non-motor symptom.

"Pain in PD is often overlooked…the good news is that it can be managed."

Jori E. Fleisher, M.D., M.S.C.E.

Fortunately, there are many ways to manage pain in PD. As with other aspects of PD, there's no one-size-fits-all approach. The first step is to work with your health care team to understand what's causing the pain and then work together to find the best treatment plan for you.

What Is Pain?

At its simplest, pain means the body hurts. When a person feels pain, nerves in the skin, joints and organs alert the brain to the location of an injury. Researchers have found that in early PD, there are already changes in the way that the body detects and regulates pain. Pain is complex, and can take many forms. In PD, pain tends to affect the side of the body where motor symptoms first appeared. If your PD started with a tremor in the right hand, you're more likely to develop pain in the right shoulder, wrist or fingers. Here are a few common types.

Musculoskeletal pain. Musculoskeletal pain is experienced by up to 75 percent of people with PD and includes pain in the muscles, bones or skeleton. It is related to rigidity and decreased movement, and to arthritis. Many people with PD experience muscle cramps and tightness in the neck, spine, and arms. Cramps in the toes or calf muscles, particularly at night or in early morning, are common. Muscles may feel sore. Joint pain, especially in one shoulder, is also common. It's not uncommon for people with PD to be diagnosed with frozen shoulder or rotator cuff problems, and even undergo surgery.

→ Tip: Keep a pain diary

For three days before your next visit to the doctor, keep a diary. Note when you took medication; when you felt like medications were working; missed doses; unusual events; when you had pain and what kind.

Dystonic pain. Do you have painful curling of your foot, toes or hands? This is dystonia, a painful muscle spasm. Up to 50 percent of people with PD experience dystonia at some stage of disease. Foot dystonia is one of the most common sources of dystonic pain in early PD. Severe, painful spasms also can occur in the neck, face or throat muscles. Dystonia may occur spontaneously or may be triggered by certain movements, but is very often experienced in the early morning. It can also be related to fluctuations in PD medications.

Neuropathic pain. Also called radicular pain, neuropathic pain occurs when a nerve is crushed or inflamed. Between five and 20 percent of people with PD experience neuropathic pain. It feels sharp, electric, tingling or like coolness or numbness. In people with PD, changes in posture, as well as dystonia, can cause nerves to be crushed. A common type is sciatica — lower back pain that extends down one leg. People with PD may also experience peripheral neuropathy — injury to nerve endings that begins with numbness in the toes or fingertips.

Central pain. Central pain affects about 10 percent of people with PD at some point. It can be difficult to describe but may include a vague, constant boring sensation; abdominal pain, reflux, shortness of breath or feeling flushed; painful sensations around the mouth, genital or rectal areas or simply "pain all over."

Treating Pain

How can you make a specialized plan for your PD pain? Build a team that includes a PD doctor, nurse, physical therapist, occupational therapist, pain management specialist and in some cases, an orthopedic specialist.

Optimize PD medications. First, it's critical to ensure your PD medications are working as well as possible. Talk with your doctor. He or she may want to examine you immediately before and after you take PD medications. He or she may increase, decrease, or change your medication to extend its effectiveness.

Exercise and physical therapy. Exercise is beneficial, particularly for musculoskeletal pain, but it can be a catch-22. It may be difficult to exercise when you're in pain, but if you're in pain and you stop moving, it gets worse! A physical therapist can recommend exercises to target the source of your pain. For example, if you experience neuropathic pain, a physical therapist can help you to improve your posture, which may alleviate pain.

Other medications. Your doctor can prescribe medications that target specific sources of pain. For example, muscle relaxants can help dystonia, as can deep brain stimulation (DBS) and botulinum toxin (Botox®). Medica-

tions for epilepsy and depression, such as gabapentin (Neurontin®) or nortriptyline (Pamelor®) may be helpful for neuropathic and central pain. Anti-inflammatory medications like ibuprofen may ease musculoskeletal pain.

Treat depression and other health conditions. Chronic pain and depression are intertwined. If a person experiences depression, it may worsen pain and other PD symptoms. In addition, people who are depressed have a hard time taking medications properly, and this sets a vicious cycle in motion: with missed doses, medications don't work well, and a person feels worse. Getting treatment for depression is essential for managing pain. It's also important to treat other health conditions — for example, osteoporosis or diabetes — that impact pain.

Alternative Treatments & Practical Tips

In seeking relief from pain, many people with PD try alternative treatments. Most of them have not been studied in clinical trials so we don't clearly understand the benefits and risks, and those that have been studied have been found equal to placebo treatments. Two that have been studied are acupuncture and marijuana.

Acupuncture. One small study suggested that acupuncture might improve sleep, but not pain, in PD. But we need larger rigorous studies to tell us more.

Medical marijuana. There have been several studies looking at the effectiveness of marijuana in treating PD. So far, the research tells us that it's *probably* ineffective and may exacerbate PD symptoms such as low blood pressure, dizziness, hallucinations, sleepiness and confusion. But it's important to remember that marijuana has 60 active ingredients, compared to aspirin, which has one! It is possible that future rigorous study of specific formulations for specific symptoms may show otherwise. We don't know enough yet. Always talk with your doctor before trying any new treatments, alternative or mainstream.

What Kind of Pain Is It?

The better you can describe your pain, the more your doctor can help. Remember "OLD CARTS":

- **O** - **Onset**: when did the pain start? Suddenly? Gradually? Yesterday? Last year?
- **L** - **Location**: where does it hurt?
- **D** - **Duration**: how long does it last?
- **C** - **Character**: is the pain achy, sharp, electric, nauseating?
- **A** - **Aggravating and Alleviating factors**: what makes the pain worse or better?
- **R** - **Radiation**: does the pain start in one place and spread elsewhere?
- **T** - **Timing**: how does the pain relate to when you take PD medications?
- **S** - **Severity**: on a scale of 1 (no pain) to 10 (hit by a truck), how much does it hurt?

Road to Recovery

Pain in PD is often overlooked, and can have a significant impact on quality of life. The good news is that it can be managed. Tell your doctor about your pain, so you can figure out what kind it is and find the right solutions for that type of pain. Once a cause is determined, you and your health care team can choose therapies that best fit your individual needs so you can feel your best.

Dr. Fleisher is Assistant Professor of Neurology and Population Health at The Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders at NYU Langone Medical Center.

Join our Upcoming *PD ExpertBriefings*

Is It Related to PD? Runny Noses, Skin Changes and Overlooked PD Symptoms
Tuesday, April 18, 1:00 - 2:00 PM ET
W. Lawrence Severt, M.D., Ph.D.
Mount Sinai Beth Israel Medical Center

Sleep and Parkinson's
Tuesday, June 13, 1:00 - 2:00 PM ET
Aleksandar Videnovic, M.D., M.Sc.
Harvard Medical School and
Massachusetts General Hospital

Pre-registration is recommended; phone participants can access each LIVE seminar by dialing (888) 272-8710 and when prompted, entering code 6323567#. CEUs are available for some professionals via PDF's sponsorship of the American Society on Aging.

This series has been made possible by educational grants from AbbVie, Inc., ACADIA Pharmaceuticals Inc. and Lundbeck LLC.

www.pdf.org/parkinsononline

fellow funded by PDF (to date, we have supported 150). In 1997, Dr. Duvoisin and colleagues broke open the field with the discovery of the first gene linked to PD: alpha-synuclein. Mutations in this gene cause PD throughout multiple generations in the rare families who carry them.

Dr. Duvoisin's finding spurred an intense search for more PD genes. Studies of families affected by PD quickly led to the discovery of another gene, LRRK2 (leucine-rich repeat kinase 2) in 2004 and the realization that LRRK2 mutations were more common in some populations than in others. For example, whereas one to two percent of whites with European ancestry carried LRRK2 mutations, these genetic changes were found in up to 20 percent of Ashkenazi Jews (people of Eastern European descent).

At about the same time, other research groups made a link between Gaucher disease and Parkinson's, shedding light on another gene: GBA. People with Gaucher disease have mutations in both copies of a gene known as GBA. Carriers of GBA (people with only one mutated copy of the gene) do not show any symptoms of the disease, but have an increased risk of developing PD.

The Most Common PD Genes

Among the 30 genetic changes that have been linked to Parkinson's disease, changes in GBA and LRRK2 are the most common. Two researchers at our Research Center at Columbia University Medical Center, Karen Marder, M.D., Ph.D., and Roy N. Alcalay, M.D., M.Sc., have pushed the field forward in understanding them.

It's important to remember that not everyone with GBA or LRRK2 mutations develops PD. So part of the research focuses on risk. "If you have the mutations, what is your risk for Parkinson's?" asks Dr. Alcalay. "That's a very important question for the family members of people with PD to know — if I have mutation, what's the risk that I will actually go onto develop PD? It's also important for research because if we develop a drug to reduce genetic risk, we first need to understand a person's baseline risk before we start trying to reduce it." For carriers of GBA mutations, Dr. Alcalay and colleagues estimate the risk of PD to be 10 percent. Dr. Marder led the work on LRRK2, finding a 30 percent risk of PD for carriers.

That was just the first step. While following the progression of PD in hundreds of people with these mutations, Drs. Alcalay and Marder observed distinct sets of symptoms associated with the two genes. For example, as a group, people with GBA mutations had more rapidly progressing PD compared to those with LRRK2 mutations, and experienced more nonmotor symptoms, including cognitive difficulties. For the majority of people with PD, it is too soon to use genetics to predict symptoms. These findings, however, represent a step in that direction.

New knowledge about LRRK2 and GBA is guiding the research of Dr. Alcalay and others into biomarkers — substances that could be measured in blood or urine to diagnose Parkinson's, monitor its progression and possibly identify genetic mutations. Biomarkers would not only ease diagnosis, they would also help clinical trials by tracking the effects of experimental therapies.

For GBA carriers, those therapies may be near at hand. "There is a lot of information about Gaucher disease, and there are treatments for it," explains Dr. Alcalay, noting that there are drugs that boost the activity of the GBA enzyme called glucocerebrosidase. "The problem is that those treatments cannot penetrate the brain. So the goals for scientists are very clear — let's try to enhance the activity of the GBA enzyme in the brain and see what happens." In fact, clinical trials for studies to do this already are recruiting participants.

"Our hope is that the research we did five years ago to identify PD genes will now lead us to studies of possible therapeutics," says Dr. Alcalay.

New Techniques

Early genetics research in PD had much success by homing in on single genes, often associated with PD in families. But genetic mutations that directly cause PD account for only ten percent of PD diagnoses. In the remaining 90 percent of cases, small changes in many genes influence a person's risk of developing PD.

More recently, scientists have taken a more big-picture approach, using a technique called genome-wide association studies (GWAS), to study hundreds and thousands of genes at one time. With the GWAS technique, scientists can scan the genomes of thousands of people with PD in search of variations — essentially single-letter "spelling" differences — associated with disease.

"The realization that all cases of PD have a genetic component doesn't mean that the disease will run in families," says Andrew B. Singleton, Ph.D., at the US National Institutes of Health. "Rather it shows us that Parkinson's occurs because of a very complex mixture of genetic changes, which likely interact with the environment to increase risk for the disease."

Dr. Singleton led a study published in 2014 that analyzed data from earlier GWAS studies to compare the genetic make-up of thousands of people with PD with the genetic make-up of healthy individuals. The researchers identified six new gene regions associated with PD. Although the PD risk associated with variations at each region was small, it was cumulative — multiple changes added up to increased PD risk. The study points to a different way to estimate Parkinson's risk and to understand how genes interact to cause the disease.

Spotlight on Populations

To date, most genetic studies on PD have been carried out on populations of European or Asian ancestry. But gene variants differ around the world. In 2009, we supported the work of Ignacio Fernandez Mata, Ph.D., of the University of Washington and the VA Puget Sound Health Care System, to create a research consortium for Parkinson's genetics called the Latin American Research Consortium on the Genetics of PD (LARGE-PD).

When Dr. Mata and team analyzed DNA collected from nearly 3,000 participants, they found some surprises. For example, says Dr. Mata, "In a European population the most common LRRK2 variant causes one to two percent of PD cases. But in a lot of Latin American countries this variant is rare, and the amount of LRRK2 carriers is tied to the amount of European ancestry people have."

When the team looked at another common PD gene, GBA, in Latin American people with PD, they discovered a new variation in Colombia (distinct from the mutations previously found) apparently traceable to the African ancestry of the participants. This variation accounted for nearly half of the GBA mutations found in this country. "This is one of the interesting things about studying populations — we are finding new variants in known genes," says Dr. Mata.

The finding is important because, in the future, if doctors want to screen Latinos for GBA variations, they will know to look for this specific one. In addition, it's possible that this variation contributes to PD in European populations too, but has not yet been detected because of its low frequency. With new funding from PDF, Dr. Mata is planning the first GWAS study in Latinos with PD, with the ultimate goal of helping to determine how gene variants affect the risk of someone of a certain ethnicity for developing Parkinson's.

Looking Ahead

Scientists have a wealth of genetic data to interpret, and they are on the cusp of using it to develop new therapies. One way this is shaping up is to allow for more focused and reliable clinical trials. It's possible that some Parkinson's disease clinical trials in the past have failed because they included a mix of participants, some of whom may be genetically predisposed to respond to a therapy and others not. Using genetics, it may be possible to develop therapies that target specific genetic variations and to recruit participants who may be more likely to benefit. In other words, we can use genetics to target the right treatments to the right people with PD.

A better understanding of genetic risks for PD will also help researchers identify subtypes of PD in the future — clusters of symptoms related to genetic variations. "Combining genetics with other factors, such as imaging, biomarkers and clinical signs, will give us the best road to predicting the course of disease, response to treatment and individualized treatment," says Dr. Singleton.

While personalized medicine is a goal for the future, it will require the difficult and costly work of studying very large numbers of people with PD. In addition, as we try to understand the mechanisms that underlie Parkinson's, studying in genetics in the lab will remain a critical way to find answers. PDF is committed to the long-term support of this research. It is only by continuing to move the field forward will we achieve our goals of better ways to diagnose and treat PD, and ultimately to end it.

GBA: Story of a Gene from Discovery to Therapy

When we identify a mutation in a gene like GBA, it can help us to understand what goes wrong to cause PD. When we know what's wrong we can try to fix it.

1987 — Researchers discover a mutation in the GBA gene that causes Gaucher disease

2003 — First hint found that mutation in GBA gene may also be a risk factor for Parkinson's

2009 — Mutations in GBA are found to be associated with 5x greater risk for developing Parkinson's*

2011 — GBA found to interact with alpha-synuclein (a protein implicated in PD) providing a possible mechanism by which the genetic mutation leads to Parkinson's

2015 — Researchers discover that targeting GBA enzyme activity may provide a possible way to treat Parkinson's*

2017 — Mutations in GBA are found to disrupt cell recycling, providing a possible mechanism by which the genetic mutation leads to Parkinson's*

2017 — Companies are developing ways to modify GBA enzyme activity to treat Parkinson's

**Denotes research funded by PDF*