

## What is PROGENI?

**P**arkinson's Research: The **O**rganized **G**enetics Initiative, also known as PROGENI, is a research effort between several research groups. Many families have been referred to the project by The Parkinson Study Group, a group of neurologists from throughout the United States and Canada, who conduct clinical drug trials for the treatment of PD. Scientists involved in the study are also located at Indiana University, the University of Rochester, Cincinnati Children's Hospital, as well as the University of California, San Diego.

The PROGENI study is sponsored by the National Institutes of Health and currently involves approximately 700 pairs of brothers and sisters throughout North America who are affected, or possibly affected, with Parkinson's disease. To be eligible to participate in this study, families must have two or more living siblings (sisters and/or brothers) affected with, or suspected of having, PD.

We would like to thank the many families who have participated in PROGENI by providing family history information and completing a Study Visit. Our hope is that through the efforts of our participants, we will one day unravel the mystery of devastating diseases, like PD. We are always eager to accept new families to help us reach this goal.

 **PARKINSON'S RESEARCH:  
THE ORGANIZED  
GENETICS INITIATIVE  
(PROGENI)**

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# PROGENI News

NEWSLETTER FOR PARKINSON'S RESEARCH:  
THE ORGANIZED GENETICS INITIATIVE

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## PROGENI CARES

### Parkinson's Research: The Organized Genetics Initiative Cares and Unrelated Subjects

By Tatiana Foroud, Ph.D., Indiana University

We believe that in the next few years, with the help of our PROGENI families, we will identify new genes that increase or decrease the risk of developing PD. Once these genes are found, it will be critical to be able to test whether they are also important in the risk of PD for individuals with PD but without a family history of PD. It will also be important to know how often people without PD might have DNA changes in these genes.

To help us address these important questions, PROGENI has initiated a new study, **PROGENI Cares**. This study is only recruiting subjects from Indiana, but we felt it was important for everyone participating in PROGENI to know about this study. PROGENI Cares is recruiting individuals from Indiana diagnosed with PD, regardless of their family history of PD. As you might expect, most people with PD participating in PROGENI Cares do not have any other family members diagnosed with PD. We are also enrolling individuals from Indiana who are over

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# Six Habits for a Highly Effective Doctor Visit

By Homer Jack Moore, M.D., Neurologist, Southern California Permanente Medical Group

- 1 Decide ahead of time what you want to accomplish.

Make a list of the most important things you want to talk about. Go over it again, and put the things about YOU at the very top.

Make sure your list is prioritized. Put the most important problems you want to discuss at the top.

- 2 Pack up all your medicines and take them with you.

It is essential for the doctor to have an accurate account of the medicines that you are taking, and how you are taking them. The most accurate means for the doctor to reliably ascertain your prescriptions is to physically look at them. Bring All medicines with you, even vitamins and herbs and eye drops.

- 3 Carry a little list of your prescriptions in your billfold or purse. Sometimes you end up seeing a Doctor when you didn't really even want to. You may end up in a strange Emergency Room somewhere; the doctor there can learn an awful lot about you and your medical history just by looking at this little list.

- 4 Drive to the doctor's office like you're going to the airport to catch a plane.

Leave plenty of time for traffic jams, flat tires, and parking lots with no parking. Carry your cell phone, just in case.

- 5 Have a conversation with your doctor.

A conversation takes place between a minimum of two people. They take turns; one talks, the other listens. Then the other one talks while the first one listens.



Hopefully your doctor listens to you while you're talking, and doesn't always cut you off. If not, find a new one. Likewise, be a good listener yourself.

- 6 Be the Captain of your own ship.

No one knows more about your symptoms than you do. No one is in a better situation to appreciate your needs than you are, not even the doctor. This would never be truer than for Parkinson's disease, which can change from day to day, or even hour to hour.

*Revised and Reprinted with permission from the Parkinson's Disease Association of San Diego: Parkinson Post April-May 2005*

# Parkinson's Disease Research

By Tatiana Foroud, Ph.D.  
Indiana University

Many individuals that I meet ask how I became involved in Parkinson's disease research. I first began to work in this area nearly ten years ago. The National Institutes of Neurological Diseases and Stroke (NINDS), a branch of the National Institutes of Health, announced that it was particularly interested in dedicating research funds for the study of the genetics of Parkinson's disease. Trained as a statistical geneticist (meaning I do primarily computer and statistical work) I was already studying another neurological disorder, Huntington's disease. My colleague and collaborator, Dr. P. Michael Conneally had worked for years

studying Alzheimer's disease. We decided that together we would try to tackle the genetics of Parkinson's disease. My only personal connection to Parkinson's disease was through my grandmother who was diagnosed with the disease late in life and who I had met only a few times when I was very young.

During the past 10 years, I have spoken at many different Parkinson's disease support group and professional meetings. At each meeting, I have talked with individuals affected by this disease and their families. Some of these people have taken part in our research studies, PROGENI and PROGENI Cares. They have shared with me their stories, and given me a glimpse into what it is like

to live with Parkinson's Disease. Their hope and optimism are amazing! I always leave each meeting with renewed respect for each person and their family who are battling this disease.

In the past seven years, PROGENI and PROGENI Cares have increased our knowledge of the genetics of Parkinson's disease. We still have a great deal to learn, but it is essential that we better understand why individuals develop Parkinson's disease so that we can design better treatments and we hope eventually find a cure. The many individuals I have met over these years inspire me to continue this important work. Thanks to all who continue to support us in these exciting studies.

## Expanding the PROGENI Study

By Cheryl Halter, M.S., CCRC  
Indiana University

As many of you know, the focus in the PROGENI study during our first 5 years was the involvement of families having two living siblings (brothers or sisters) with Parkinson's disease (PD). From the study of over 700 families meeting this criterion, we have identified several different chromosomes that might be important in the risk for PD. We are now eager to expand our studies so that we can find the genes on these chromosomes that increase or decrease the risk for PD.

To accomplish this goal, we are now asking certain families to allow us to contact more family members and include them in the PROGENI study. Genetic studies are most informative when we study families with many members diagnosed with PD. Among our 700 PROGENI families are over 225 families with

what we call a 'very strong family history of PD'. We define these families as those reporting four or more members with PD, or families in which one of the parents of the sibling pair with PD is also reported to have had PD. In families meeting one of these criteria, we have begun asking all the brothers and sisters of the siblings with PD to participate in the PROGENI study. In some cases, we are asking the children of people with PD to participate in the PROGENI study as well.

In these families with a 'very strong family history of PD' we are asking specific family members to undergo the same clinical examinations as their brothers and sisters with PD. This includes a brief neurological examination, answering some general health and history questions, and a blood draw. Information from these newly

studied family members will allow us to make some comparisons between those with PD and those without.

If your family meets the 'very strong family history of PD' criteria and you have not yet heard from us, you will soon. We hope that families who do not meet these new expanded study criteria understand that they also continue to be very important for the PROGENI study. We want to keep learning more about your family history, whether any family members are showing symptoms of PD or have been newly diagnosed with PD, and we are always eager to include you in our autopsy program.

If you have any questions about the expansion of the study, or PROGENI in general, please call Cheryl Halter at 888-830-6299 or by email at [chalter@iupui.edu](mailto:chalter@iupui.edu).

# Parkinson's Disease and Parkinsonism

By Larry Elmer, M.D., Neurologist, Medical University of Ohio



Frequently, Parkinson's disease (PD) specialists (also called movement disorder specialists) are asked to comment on whether a particular person's symptoms of PD will progress rapidly or slowly. Patients and their families also wonder how long their symptoms can be controlled with medications or whether surgeries such as deep

brain stimulation would be effective. At the initial onset of PD like symptoms, these questions may be particularly difficult to answer - what follows is a brief discussion of the difficulties in separating true PD from imitators, the so-called **Parkinson's plus syndromes** (PPS).

Parkinsonism is not necessarily a single disease - the word "parkinsonism" refers more to a constellation of symptoms. This symptom complex is best described with words like bradykinesia (slowness of movement), rigidity (stiffness of the joints with passive movement), rest tremor and postural instability (difficulty with balance associated with walking, turning and/or while standing or sitting still). These words and the symptoms they describe may be associated with a whole host of disorders. The most common of these disorders is what we refer to as **idiopathic Parkinson's disease** (IPD). IPD is frequently treatable using current regimens that increase and/or maintain levels of brain dopamine. This is due to the fact that the primary problem in IPD is a loss of nerve cells in the brain that use dopamine to communicate with other nerve cells.

Unfortunately, there are other diseases that mimic IPD and confuse physicians, patients, and their families with symptoms that are nearly indistinguishable from IPD at initial onset. Because of the confusion associated with accurate diagnosis, patients who have PPS usually are treated with the same agents given to IPD patients. The challenge of dealing with these imitators emerges when individuals with PPS don't respond to the typical dopamine-replacement strategies or don't respond to treatment in a dramatic fashion typical for someone with true IPD. The reason the PPS patients don't benefit dramatically is due to the fact that other brain areas -

involving different brain chemicals other than just dopamine - are also affected in PPS. Now, let's look at some of the more common mimics of IPD.

**Multiple system atrophy** (MSA) is the prototype of a PPS. Sharing clinical similarities with IPD, MSA nevertheless presents with a constellation of symptoms that may be described as a "superset" of a typical IPD presentation. Three major classes of MSA have been described:

**MSA - P** (P=Parkinsonism): Also referred to as **striatonigral degeneration** (SND), this variant typically presents with classic features of parkinsonism which is virtually resistant to the clinical benefits of dopamine-replacement therapy. This syndrome is notoriously difficult to distinguish from IPD at initial evaluation, where patients may have slight but subjective (and sometimes mildly objective) symptomatic improvement from dopamine-replacement therapy, only to later progress to limited, if any, reproducible or demonstrable benefit from conventional anti-parkinsonian therapies. Recently, a dramatic and emotional TV presentation aired, highlighting the life of Milly Kondracke, who was afflicted with MSA-P. Milly, along with her husband Mort, tirelessly advocated Parkinson's research and care. Her case illustrates the difficulty of obtaining an accurate clinical diagnosis as well as the intractable progression of this disorder.

**MSA - C** (C=Cerebellar): This variant is also referred to as **olivopontocerebellar atrophy** (OPCA). Sometimes presenting initially with parkinsonian features, individuals afflicted with OPCA may develop preceding, concomitant or subsequent features of cerebellar dysfunction, which frequently causes difficulty with coordination, balance and slurring of the speech. OPCA will sometimes respond to medications for IPD, but the cerebellar features are difficult, if not impossible, to treat.

**MSA - A** (A=Autonomic): Commonly referred to as Shy-Drager-Syndrome (SDS), this form of MSA

typically presents with parkinsonian features and associated autonomic dysfunction. The autonomic nervous system controls most of our unconscious nerve activity such as blood pressure, heart rate, sweating, movement of our intestines, and much, much more.

The autonomic dysfunction in SDS includes, but is not limited to: orthostatic hypotension (drop in blood pressure with upright posture), urinary retention or incontinence, sweating disturbances, profound difficulty with constipation and/or impotence (in males). As in OPCA, sometimes the parkinsonian features in this disorder respond to dopamine-replacement therapy, but the autonomic features are extremely difficult to treat.

**Progressive Supranuclear Palsy (PSP)** is another PPS. In contrast to the MSA disorders mentioned above, when one looks at the post-mortem brain changes under the microscope, PSP shares similarities with Alzheimer's disease (AD), frontotemporal dementia (FTD), corticobasal ganglionic degeneration (CBGD) and others. The symptoms of PSP are typically early gait disturbance, bradykinesia, rigidity, and occasionally, tremor. It is most commonly misdiagnosed as IPD early in its onset. Relentlessly progressive, PSP usually leads to increasing severity of gait and balance disturbances, difficulty with speech and swallowing as well as a profound disturbance of eye movements. Like many of the other imitators of PD, PSP shares the clinical characteristic of being poorly responsive or totally unresponsive to dopamine-replacement strategies.

While the preceding list may look like an alphabet soup, each of the disorders listed above have characteristic pathological changes and typical areas of the brain involved. Due to the difficulty in diagnosing these disorders during life, the formal and accurate diagnosis is sometimes only made after death when a pathologist examines the brain. These disorders usually also have typical clinical manifestations, but these clinical features may not be easily distinguishable from IPD in the early stages. In other words, when someone walks into a doctor's office with "parkinsonism", it may not be entirely clear – even to a specialist –

“ **Parkinsonism is not necessarily a single disease – the word “parkinsonism” refers more to a constellation of symptoms.** ”

what the true, final diagnosis will be. This dilemma is complicated by the fact that currently there is no commercially available blood test or x-ray available that clearly and easily distinguishes PPS from IPD. For that reason, most specialists will treat individuals with symptoms of “parkinsonism” using

the typical therapies for IPD – the so called “therapeutic trial” – in order to evaluate their response to treatment. This is not a perfect test since some patients with IPD demonstrate variable (i.e., less than dramatic) benefit from different doses and/or combinations of currently available therapies. To add to the confusion, some PPS patients will experience some benefit from typical dopamine-replacement strategies, although rarely is this benefit dramatic. There are many other disorders that qualify as Parkinson-plus syndromes. The two final entities mentioned below would not meet the true definition of a PPS, however, they are common enough to deserve discussion in this article.

**DLB – Dementia with Lewy bodies:** The clinical symptoms of DLB are sometimes very similar to Parkinson's disease with dementia (PDD). Dementia is a term used to describe abnormalities in memory, clarity of thinking, language function and/or the ability to process information. It can also be associated with changes in behavior and/or personality. People with typical PD may develop symptoms of dementia after many years of dealing with their IPD. DLB is different, in that the cognitive (memory and thinking aspects) of this disorder present almost simultaneously with the parkinsonism.

There is extensive clinical overlap of DLB with other dementia disorders such as Alzheimer's as well as with IPD and the PPS diseases. The combination of parkinsonism and early dementia suggest the possible diagnosis of DLB, however, the symptoms of parkinsonism may be delayed by months or longer. Symptoms characteristic of DLB include fluctuations in motor function and cognition that do not clearly coincide with the person's medication dosing schedule. Some DLB patients respond to medications used for IPD, but some do not clearly achieve a symptomatic motor benefit (such as improvement in mobility). Patients may have fainting-like spells where they become unresponsive or even unconscious for

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# Parkinson's Disease and Parkinsonism Continued from page 5

brief periods of time. Visual hallucinations and/or delusions (sometimes prior to the administration of dopamine-replacing medications and frequently associated with the use of those medications) are common in DLB. A characteristic sleep disturbance, REM sleep behavior disorder in which the person acts out their dreams, is very common in DLB patients and may precede cognitive and motor changes by years. However, it is not uncommon for IPD patients to frequently have this symptom, as well. DLB patients may demonstrate exquisite sensitivity (unresponsiveness, severe rigidity) to older, stronger anti-psychotic medications, prohibiting their use. Patients with DLB may also develop myoclonus (jerking movements of the arms and/or legs) as well as significant autonomic changes (see above MSA-A section).

**NPH** - Normal Pressure Hydrocephalus: The clinical symptoms of NPH can mimic the symptoms of IPD, especially with regard to slowness and difficulty in walking as well as with changes in cognition. NPH received large amounts of attention following the airing of a commercial describing this condition during the Super Bowl in 2005. In that video, a gentleman who was severely disabled with regard to his gait and thinking demonstrated dramatic improvement after being treated for NPH.

While the treatment for NPH shares nothing with the treatment for IPD - typically a shunt is surgically placed inside the ventricles (fluid filled sacs inside the brain) in order to drain out excess fluid. This sometimes results in dramatic improvement in the more common aspects of NPH such as gait disturbance, slowing of the mind and body, as well as urinary frequency, urgency and/or incontinence. Falling and balance disturbances can also plague individuals with NPH. Due to the progressive nature of this disorder, it is important to have this diagnosis considered, especially if someone has been diagnosed with IPD, and yet are not having a typical

“ **Our hope for the future is that treatments that stop or significantly slow the progression of these disorders will also emerge, providing the opportunity for people afflicted with these diseases to live with minimal disability and without concern for future worsening of their symptoms.** ”

beneficial response from dopamine-replacement therapy.

In summary, the diagnosis of PPS is difficult to make, especially in the early stages of all forms of “parkinsonism”. The concept of a therapeutic trial, using dopamine-replacement strategies (or other occasionally effective treatments for IPD), is one of the ways to help distinguish IPD from PPS. There are many causes of PPS, only some of which are mentioned here. There are also other disorders, such as DLB and NPH that can mimic the symptoms of IPD but have other reasons for their symptom complex and other strategies for treatment. Finally, there are many other causes of parkinsonism - such as medications (haloperidol, metoclopramide, risperidone, to name a few) - that need to be considered in the differential diagnosis of anyone who presents to a doctor's office with symptoms of parkinsonism.

Thankfully, most diseases causing PPS are rare. Unfortunately, they remain difficult to treat and to diagnose, leading to confusion and frustration on the part of the patient, the family and commonly the treating physician. Our hope for the future is that treatments that stop or significantly slow the progression of these disorders will also emerge, providing the opportunity for people afflicted with these diseases to live with minimal disability and without concern for future worsening of their symptoms. In the meantime, individuals who think they may be dealing with PPS should seek out a specialist in movement disorders. This can help patients and their families understand why particular problems are occurring or why there is lack of a clear medication benefit, which typically occurs in IPD. Most of all, dealing with a specialist in movement disorders (which includes IPD and all forms of PPS), will provide the best opportunity to learn as much as possible about these disorders and to prepare for the inevitable challenges we face in dealing with these problems.

# Coordinator's Corner

## Getting to Know the PSG Coordinators

**Stephanie Wilson, RN** Site: Medical University of Ohio

**Q How long have you and Dr. Elmer been doing PD research?**

**A** Dr. Elmer has been at the Medical University of Ohio since 1998 and I have been here since May 2002.

**Q How many PD patients do you see in a day? a week?**

**A** Dr. Elmer currently has about 800 patients that he is treating. We usually see about 25 patients a week.

**Q How many PROGENI Study Visits have you done?**

**A** We have done 34 visits at this site. I have done 13.

**Q What is your favorite part of the Study Visit?**

**A** I enjoy getting more personal information from the subject, background information about where they have lived and the work they have done. The visits often stir good memories for the subjects and they get a chance to share good things about their life.

**Q What do you like most about your involvement with PROGENI? Why?**

**A** It is exciting to give patients an opportunity to contribute to finding out more about how to treat or prevent PD. The patients are usually very excited about the study and it often helps them connect with their siblings by sharing the study visit experience.

## A Guide to Parkinson's Disease Medical Terminology

By Kathleen K. Miller, C.O., CCRP

A visit to the neurologist can be just as confusing and frightening as the diagnosis and understanding of Parkinson's disease. During the neurological exam many medical terms will be used to describe the findings of someone who has Parkinson's disease.

Below is a list of common medical terms and their meanings which may make your exam visit less confusing and give you a better understanding of the disease:

**Akinesia:** Inability to move ("freezing") or difficulty in beginning or maintaining a body motion.

**Ataxia:** A mobility-impairment condition marked by loss of balance and decreased coordination.

**Bradykinesia:** The slowing down and loss of spontaneous and voluntary movement.

**Cogwheeling:** A jerky or ratchet-like sensation felt by a physician when a patient's limb is moved around a joint.

**Dysarthria:** Slurred or otherwise impaired speech.

**Dyskinesias:** Involuntary, uncontrollable, and often excessive movement. These movements can be lurching, dance-like or jerky, and are distinct from the rhythmic tremor commonly associated with Parkinson's disease. A common side effect of many drugs used to treat Parkinson's disease.

**Dysphagia:** Difficulty in swallowing.

**Dystonia:** Abnormal and awkward posture or sustained movements of a hand, foot, or other part of the body; may be accompanied by rigidity and twisting.

**Freezing:** Abrupt and temporary inability of Parkinson's patients to move that frequently occurs

at a boundary such as a door or when exiting a car.

**Neurodegenerative:** Refers to conditions such as Parkinson's that are characterized by the loss of cells in the central nervous system.

**Rigidity:** Abnormal stiffness in a limb or other body part. It is most apparent when an examiner moves a patient's limb – as in cogwheeling.

**Tremor:** Unwanted rhythmic movements (may be fast or slow) that may affect the hands, head, voice or other body parts.

**Wearing Off:** Loss of effectiveness of Parkinson's medications between doses. If the effectiveness of a medication does not last until the next dose is due, it "wears off".

Sources: *Stedman's Medical Dictionary (26th edition)*

[www.michaeljfox.org](http://www.michaeljfox.org)

## **PROGENI Cares** Continued from page 1

the age of 65, and do not have any neurological disorders such as strokes, Alzheimer's disease or Parkinson's disease. These individuals are called healthy, normal controls and will be used as a comparison group to those with PD. Everyone participating in PROGENI Cares, the individuals with PD and the healthy controls without PD, are completing the same clinical evaluation that everyone in PROGENI has completed. This includes a brief neurological examination, answering some general health and history questions, and a blood draw. Our free and voluntary autopsy program is also available to everyone participating in PROGENI Cares.

Including individuals with PD who do not have a family history of the disease allows us to better understand the DNA changes that we find in our PROGENI families who have at least 2 siblings with PD. Genes that are important for the risk of PD in individuals with and without a family history of PD may be very important targets for future medications designed to slow or delay the onset

of the disease. Including healthy controls is also important. We need these healthy individuals to help us determine if the DNA changes we find in patients with PD are also found in individuals who don't have PD. This is an important question to answer when considering future genetic tests.

Our PROGENI families have provided us many important clues to the genetics of PD. As we have discussed in previous newsletter issues, our 700 families have helped us to better understand the role of the parkin (PARK2) and the leucine-rich repeat kinase 2 (LRRK2, PARK8) gene (Vol. 3 Winter 2003, Vol. 5 Winter 2005.) In future issues, we will be telling you about research progress in both PROGENI and PROGENI Cares.

If you reside in Indiana and have PD but no sibling with PD, or if you are over the age of 65 and have no neurological disorder, please contact Kathleen Miller at 317-278-6158 or 888-830-6299 for information about enrolling in PROGENI Cares.

## **Useful Sources for Information and Support**

### **The American Parkinson Disease Association (APDA)**

<http://www.apdaparkinson.org>  
Tel: 718-981-8001 or 800-223-2732

### **The Michael J. Fox Foundation for Parkinson's Research**

<http://www.michaeljfox.org>  
Tel: 800-708-7644

### **National Parkinson Foundation**

<http://www.parkinson.org/>  
Tel: 305-547-6666 or 800-327-4544

### **Parkinson's Disease Foundation (PDF)**

<http://www.parkinsons-foundation.org>  
Tel: 212-923-4700 or 800-457-6676

### **Parkinson Disease Information and Resources**

[www.pslgroup.com/PARKINSON.HTM](http://www.pslgroup.com/PARKINSON.HTM)

### **The Parkinson Study Group (PSG)**

<http://www.parkinson-study-group.org/>

### **World Parkinson Disease Association**

<http://www.wpda.org/>  
Tel: [39] 02 66713111 (Italy)

### **Parkinson's Action Network (PAN)**

[info@parkinsonsaction.org](mailto:info@parkinsonsaction.org)  
<http://www.parkinsonsaction.org>  
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