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## NEW PROGENI PUBLICATIONS

By Tatiana Foroud, Ph.D., Indiana University

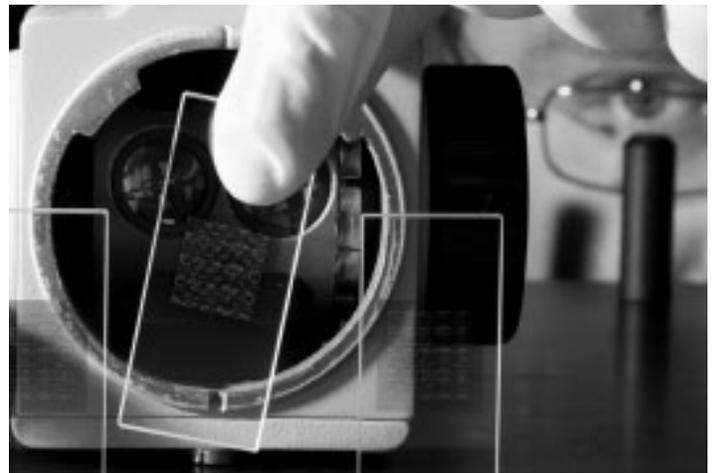
The genetics of Parkinson's disease (PD) is proving to be quite complicated. As a result, it is critical for studies like PROGENI to carefully investigate each gene that is reported to be potentially important in the genetics of PD. In the past few months, PROGENI has published three papers on the LRRK2 and DJ-1 genes that have addressed this important question.

### LRRK2

In our last issue of this newsletter, we discussed the gene called LRRK2, which stands for leucine-rich repeat kinase 2. This gene codes for a protein called dardarin. To date, one particular DNA change (mutation) in the LRRK2 gene, called G2019S, has been shown to be the most common defect in the more typical late onset PD, particularly in Caucasian samples. Other DNA defects have been reported to be quite common in the Han Chinese population and in a small community in the Spanish Basque region.

One important question to address is whether or not other DNA changes in the LRRK2 gene can cause PD. If a DNA change causes disease, we call it a mutation. It is important to note that many changes in our DNA sequence do not alter the way the protein is made or how it functions and therefore do not cause disease. These DNA sequence changes are typically not called a mutation.

In one recently published paper, the PROGENI study investigators tested 12 other reported DNA mutations in the LRRK2 gene. While they examined 430 families, they found only one family which had any of these 12 mutations. From this large amount of data, the PROGENI investigators were able to show that these 12 mutations were quite rare in Caucasian patients with familial PD.



In a second paper, the PROGENI investigators examined another DNA sequence change in the LRRK2 gene that was thought to potentially cause PD. We tested a large number of DNA samples from PD patients as well as individuals who do not have PD. We found that this particular DNA change in the LRRK2 gene was no more common in the PD patients than it was in the healthy, normal controls. As a result, the PROGENI study investigators were able to show that this particular DNA sequence change, called R1514Q, is unlikely to be a functional mutation or cause PD. Being able to show that a DNA sequence change does not cause PD is nearly as important as demonstrating that a change does cause PD. This information is critically important when diagnostic testing of the LRRK2 gene

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> To read past issues of the *PROGENI* Newsletter or any of our scientific publications, please visit <http://progeni.iu.edu/Publications/index.asp>.

# What is PROGENI?



**P**arkinson's **R**esearch: The **O**rganized **G**enetics **I**nitiative, 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 and PROGENI Cares studies are sponsored by the National Institutes of Health. PROGENI currently involves over 800 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. PROGENI Cares now includes more than 500 individuals with PD and their healthy controls.

We would like to thank the many families who have participated in PROGENI and PROGENI Cares 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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# National Institute of Neurological Disorders and Stroke

By Claire Wegel, MPH  
Indiana University

As you may be aware, the PROGENI study receives its funding through the National Institutes of Health, more specifically the National Institute of Neurological Disorders and Stroke (NINDS). The Institute was created by Congress in 1950 to support and conduct research on the more than 600 disorders that affect the nervous system with the mission of reducing the burden of neurological diseases. Because Parkinson's disease is the second most common neurodegenerative disorder, one of NINDS' main priorities is Parkinson's disease research.

In our continued efforts to increase knowledge and understanding of the genetic causes of Parkinson's disease, the PROGENI study has begun contributing newly drawn blood samples to the National Institute of Neurological Disorders and Stroke Human Genetics Resource Center. The PROGENI Cares

study has been contributing samples to the repository since the study began.

The goal of the Human Genetics Resource Center is to develop genetic resources that can be shared by the research community, and to encourage research efforts. While the repository does make genetic and general health information available to all researchers, participant confidentiality is closely guarded, and no personal identification information is shared. Several PROGENI sites, starting with the Indiana University Medical Center, have already begun sending samples to the NINDS Human Genetics Resource Center. Our goal is to have all 50 PROGENI sites contributing samples to the Repository over the next few months. With all PROGENI sites contributing genetic material to this effort, we can support further research into the causes of PD.

*For more information on NINDS or the Human Genetics Resource Center, please visit their website at <http://www.ninds.nih.gov>.*

# HOUSE CALLS

By Deborah Hall, M.D.  
University of Colorado Health Sciences Center



The sun was setting on the Western plains. Various shades of color were layered on the horizon. As the sun set, I could feel myself also begin to fade somewhat despite being behind the wheel. We were in the middle of one of our many journeys to see research patients in the Rocky Mountain region. I was traveling with a genetics counselor named Cathlin. We had begun to master the routine of packing up our supplies and going on the road – me with my doctor bag, history and exam forms, and questionnaires; and Cathlin with her pedigree charts, consent forms, and blood kits. As both of us are from suburban areas, we were quickly educated in the way of Western life. We would have meals in rural towns, discovering (by luck) restaurants specializing in steak and homemade pie. We became familiar with Western crops and began to understand the distances between pockets of civilization in the rural plains. Having spent only minimal time in rural areas during training, I was quickly learning about the lack of medical facilities for hundreds of miles and subsequently, lack of resources for uncommon diseases for most of our research families. We were studying a newly diagnosed genetic disorder that typically affects at least three generations in our research families. Making home visits seemed to make sense in this population due to the high number of affected family members. Travel across the west, especially in the winter, was difficult for these families as it required families to travel with affected children and their affected grandparents.

During our first house call, we realized how unusual it was for physicians and counselors to go into the homes of their patients. We were welcomed into the home and greeted with a large spread of food. We were given a tour of the house and introduced to the family. Eventually, we would consent the subject, examine him/her, and do a videotape protocol. We would end with some chatting about various topics – issues related to the disease, medications,



**“...I wished that all young investigators of genetic disease had the opportunity to experience the disease and its ramifications in such a close way.”**

current research in the field, etc. This would be followed by a mad dash to deliver the blood samples to Federal Express. Our trip to Nebraska was more like a town visit, rather than a home visit. We went on Labor Day weekend, hoping to see as many of the biological family members as possible. The town was small - there was no stop light and only one main road. The family had gotten permission to use a medical clinic, free of charge, once used by the only primary care physician in the area (and who no longer came to town). The rooms contained equipment that appeared to be dated to the 1950s, but it was all functional. Upon arrival into the town, we went straight to the home of our research family. They welcomed us at our car and escorted us into a very lively home, with wonderful aromas and animated conversations. We sat down to dinner with the family for the first of many meals over a four day period, telling them about our lives and our work.

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# Autopsy: An Important Part of Our Research

By Tatiana Foroud, Ph.D.  
Indiana University

The word "autopsy" is derived from the Greek word *autopsia*, which means to see with one's own eyes. An autopsy is the examination of brain tissue by a pathologist with special training in the area of neurological disorders, such as Parkinson's disease. The pathologist looks for changes in brain tissue that would only occur in an individual with Parkinson's disease.

While it is often difficult to decide to pursue an autopsy of a family member, there are several important reasons to consider this option. First, a post-mortem examination of the brain is the only way to definitively diagnose Parkinson's disease. Second, information obtained through an autopsy may provide family members with essential information, particularly in the case of hereditary diseases. Third, the autopsy procedure provides additional tissue samples for research into the causes and mechanisms of the disease.

Many families are reluctant to discuss an autopsy and wait until the last moment to do so. The time

when a family member passes away is filled with many emotions as well as the need to carry out any arrangements and notify the necessary individuals. By having the autopsy planned well in advance, this time will not have the added stress of deciding whether or not to have an autopsy done, contacting all of the individuals needed to make the decision, and alerting the appropriate physicians.

Coping with a degenerative illness affecting a family member is emotionally difficult as is the decision to prearrange an autopsy; however, it is important for both the family and the community. We will pay all costs associated with the autopsy such as transportation of the body, brain tissue removal, and neuropathological examination of the tissue.

PROGENI staff members can discuss autopsy with you and answer any questions that you might have. We can work together to plan the autopsy and ensure that the opportunity to gain this valuable family medical information is not lost.

For further information, please contact Sue Fox (PROGENI) or Claire Wegel (PROGENI Cares) at 1-888-830-6299.

## House Calls

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We immediately were welcomed into their home despite being complete strangers. The trip continued in the same manner as we saw each of the family members in the borrowed clinic. Recruitment was very high as each of the family members headed over from the main house at their 'appointment' time.

Having just finished residency and still catching up on sleep, I did not initially recognize the uniqueness of our current situation. Over the next four days, we became part of the family reunion. We began to understand the stress of having a neurological disease and the toll it took on family relationships. At the end of our stay, we were invited to the Labor Day parade and

given a prime position to watch on Main Street. As the dancing horses and small floats went by, we felt we had a better understanding of what happens to families with inherited disease: how the disease starts with a single mutation, but then expands to reach out generation after generation. As we watched in awe as a horse picked up a hat from the ground and tossed it to its rider, I wished that all young investigators of genetic disease had the opportunity to experience the disease and its ramifications in such a close way.

*Dr. Hall is a movement disorder specialist at the University of Colorado Health Sciences Center in Denver Colorado. She has conducted field visits as part of the PROGENI study, as well as other research studies*

# Participating in Clinical Research

By Claire Wegel, MPH  
Indiana University

For many people, there is a feeling of helplessness that comes with being diagnosed with a degenerative neurological disease. This feeling is often shared by those closest to the patient - their family and friends. Participating in clinical research is one way that individuals with Parkinson disease (PD) and other neurological diseases can take an active role to strike back against their illness. This outlet is not always available to their loved ones. However, researchers are now beginning to realize that individuals without PD may be just as important to PD research as individuals with the disease.

Very little is known about healthy aging. Using healthy volunteers as a comparison to persons with Parkinson or Alzheimer's disease (AD) not only tells us about those diseases, but tells us about healthy aging as well.

As we learn more about the genetics of diseases like PD and AD it has



become crucial to include healthy individuals in the research to help us answer questions, such as

- Do people without PD carry a certain genetic variation found in PD patients?
- How important is a particular gene in causing PD?
- Do people with sporadic PD have similar genetic profiles as people with familial PD? And people without PD?

To work toward increasing our understanding of the genetics

of PD, both the PROGENI and PROGENI CARES studies include individuals without PD. PROGENI has begun inviting siblings who do not show symptoms of PD to take part in the project, and the PROGENI CARES study encourages spouses and friends who don't have PD or a family history of PD, to join the research effort.

■ If you are the spouse or friend of someone with PD and live in central Indiana, please call Claire Wegel at 1-888-830-6299 for more information on how you can get involved in PROGENI CARES.

■ If you are ineligible to participate as a healthy control in PROGENI CARES because of a family history of PD, you may still be able to get involved in clinical research for other neurodegenerative diseases, like Alzheimer's disease. If you live in the Indianapolis area and would like to learn more about participating as a healthy control in the Genetics of Late-Onset Alzheimer's study, please call 1-800-526-2839.

## New PROGENI Publications > continued from page 1

is being considered. It is essential that we are able to accurately tell patients and their families which LRRK2 DNA sequence changes can cause PD and which are unlikely to increase the risk for PD.

### DJ-1

The PROGENI investigators also tested a gene that was identified a few years ago, called DJ-1. DNA mutations in this gene have been shown to cause PD. However, they appear to be quite rare. The PROGENI investigators thought it was important to test how rare these mutations were in a sample of familial PD patients. After prioritizing which samples to test, a list

of 93 PD patient samples was selected for detailed testing. No DNA sequence changes (mutations) were found in any of the 93 PD patients who were tested. From these results, we were able to conclude that mutations in DJ-1 are unlikely to be an important cause of familial PD.

It is with the continued support of PROGENI families and PROGENI Cares subjects and controls that important papers such as these are possible. Your involvement in this type of genetic research is vitally important to unraveling the mysteries of Parkinson's disease. Thank you.

# More Research Sites Join the PROGENI Effort

We would like to take this opportunity to welcome three new investigators and coordinators to the PROGENI research effort. **Dr. Padma Mahant** and **Ms. Elizabeth Karoll**, Banner Good Samaritan Medical Center, Phoenix AZ; **Dr. Michael Rezak** and **Ms. Gina Medalle**,

Evanston Northwestern Healthcare, Evanston IL; and **Dr. Richard Zweig** and **Ms. Rhonda Feldt**, LSU health Sciences Center in Shreveport, Shreveport LA. The addition of these sites brings the total number of PROGENI research facilities to 49.

## New PROGENI Cares Coordinator

**Claire Wegel**, who recently received her Master's degree from the University of Minnesota's School of Public Health, joined the PROGENI team in September as the new coordinator for PROGENI Cares. Claire brings three years of health research experience to the study, having worked on epidemiologic studies of cervical cancer, melanoma, and cardiac events as well as community studies of smoking and alcohol policy.

If you have any questions about the PROGENI Cares study, please feel free to contact Claire at (317) 278-6158 or toll-free at (888) 830-6299 or by email, [cwegel@iupui.edu](mailto:cwegel@iupui.edu).



## 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.pdf.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] 02 667.13.111 (Italy)

### Parkinson's Action Network (PAN)

[info@parkinsonsaction.org](mailto:info@parkinsonsaction.org)  
<http://www.parkinsonsaction.org>  
Tel: 800-850-4726 or 202-842-4101  
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