PROGENI News

Newsletter for Parkinson's Research:
The Organized Genetics Initiative

Volume 3 • Winter 2003

What is PROGENI?

Parkinson's **R**esearch: The **O**rganized **Gen**etics **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 in both San Diego and Irvine.

The PROGENI study is sponsored by the National Institutes of Health and currently involves approximately 450 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)

Department of Medical
and Molecular Genetics
975 West Walnut Street
Suite 130
Indianapolis, IN 46202-5251

Phone: 1-888-830-6299

Email: chalter@iupui.edu
or kmiller4@iupui.edu

PROGENI Funded by NIH For Another Five Years!

By Tatiana Foroud, Ph.D. - Indiana University

The PROGENI study was originally funded by the National Institutes of Health (NIH) for five years with the goal of identifying 600 siblings (brothers and sisters) with Parkinson disease (PD). The families participating in this important study will allow researchers to begin to identify the genes that increase the risk that an individual will develop PD. The PROGENI study has been ongoing for five years and has met all of its initial goals. More than 600 pairs of siblings have participated in the study. With this information, we have been able to learn more about the genetics of PD.

Because of the important successes of our first five years, the NIH has decided to fund the PROGENI study for another five years. During this time, we will be continuing to recruit siblings with PD. In addition, we will also be asking family members who have completed the study to consider a brain autopsy. Through the examination of brain tissue, researchers can better understand the changes that occur in individuals with symptoms of PD.

We have a staff member, Elizabeth Riley (1-888-830-6299), available to help the families who have participated in PROGENI, plan for autopsy.

Continued on page 2

Health Insurance Portability and Accountability Act (HIPAA)

By Cheryl A. Halter, MS – Indiana University

If you have been to see a health care professional in the US within the past 9 months you are probably aware that the federal government as enacted legislation to try to protect people's personal health information. The Office for Civil Rights is the department responsible for implementing and enforcing these privacy regulations. As reported on the official DHHS website devoted to HIPAA, (http://www.hhs.gov/ocr/hipaa/bkgrnd.htm) the HIPAA Privacy Rule of1996 for the first time creates national standards to protect the medical records and other personal health information of individuals. For patients it means being able to make informed choices when seeking care and reimbursement for care based on how personal health information may be used.

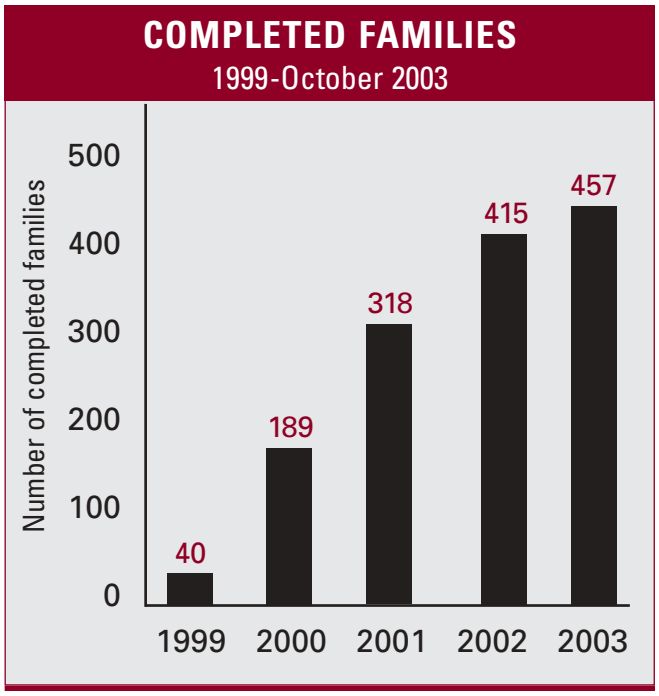
For research participants, it means that we have implemented another level to our protection of your family history information. When enrolling in PROGENI, US subjects enrolled after April 14, 2003 have been asked to sign a Release of Health Information for Research form. In the coming months, subjects enrolled before this date will also be asked to sign this form. We are doing this to help ensure that all subjects are covered under this extra protection. So, when you receive a yellow Release form, please read it and sign where indicated. **If you have any question about the form, please give us a call at 1-888-830-6299.**

PROGENI Funding

Continued from page 1

The PROGENI study will also be expanding its focus in Indiana. For the first time, we will also be asking individuals diagnosed with PD, but without any other family members with the disease, to consider participating in the PROGENI study. Each of these subjects will be asked to help us identify an unaffected "in-law" who is unrelated to them, but is the same gender, age and ethnic background. The participation of these subjects will make it possible for us to determine which genes important in familial PD are also risk factors for individuals without a strong family history of PD. These subjects will be recruited only from the state of Indiana.

As we have in the past, we will continue annual contact with all family members who have participated in the PROGENI study. This allows us to keep families updated on the progress of the study and to learn about changes within the family. It is important for us to learn about any family members who may have begun to show symptoms of PD, or who may have recently been diagnosed with PD. Additionally, we appreciate being informed of any deaths within the family. This year, there may also be an additional form that some families may receive. The US Federal Government has recently implemented some policies in an attempt to further safeguard people's personal health information. This formis designed to address these policies.



If you receive a yellow Authorization for Release of Health Information, please read it, sign it in all indicated places and return it with your update form.

Throughout this newsletter, you will be learning of the progress already made in the PROGENI study. We thank you for your ongoing participation in this important research project. Through your family's participation in this study, we will learn more about the genetic risk factors that increase an individual's risk for PD.

Coordinator's Corner

By Robert Bowman, Indiana University

As part of our ongoing series on a day in the life of a study coordinator we are eager to share information from two coordinators participating in the PROGENI study.

Julie So, RN

Toronto Western Hospital

How long have you and Dr. Lang been doing PD research?

Six years.

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

About ten patients a day, around 50 patients a week.

How many PROGENI Study Visits have you done?

15 Study Visits, 6 completed families

What is your favorite part of the Study Visit?

Being able to communicate and talk to the patients and hear what they have gone through in their life.

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

Finding the genetic link to PD and thereby helping future patients.

Brenda Pfeiffer, RN, BSN

University of Tennessee-Memphis

How long have you and Dr. Pfeiffer been doing PD research?

I've been working with PD for 5 years and Dr. Pfeiffer has been doing it for over 20 years.

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

Between 6-10 in a week

How many PROGENI Study Visits have you done?

28 Study Visits, 10 completed families.

What is your favorite part of the Study Visit?

Interviewing the patients and hearing about their lives, their families, and their relations and how PD affects them.

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

Being involved in finding the hereditary involvement.

Autopsy update

By Cheryl A Halter, MS Indiana University

We continue to have good response to our offer to plan autopsies for individuals who have completed PROGENI Study Visits. Each autopsy plan is unique, tailored to each person's particular family and living situation.

The key components of an autopsy plan require identification of a facility for removing the brain tissue at the time of death, and a facility to examine that tissue. These facilities may be the same location but many times are not. We cover all costs associated with autopsy so we work closely with each family to identify local resources. We may need to contact funeral and/or nursing homes to complete the plan. When planning is complete, we provide family members with an outline of who should be contacted at the time of death to ensure that the autopsy proceeds without difficulty. To date, autopsies have been completed on nine PROGENI subjects and reports are pending on six more. An additional 32 autopsies have a final plan in place. This means that all the components necessary to perform an autopsy have been put in place for 32 individuals. Another 18 individuals are currently finalizing their autopsy plans.

If you are interested in planning an autopsy for yourself or a family member we encourage you to plan ahead. Please give Elizabeth Riley a call at 1-888-830-6299 if you would like more information. We will be happy to discuss autopsy with you and to help put a plan in place.

Genetics an Important Area of PD Research

By Tatiana Foroud, Ph.D. - Indiana University

During the past decade, many scientists have been carefully examining the role of genes in Parkinson's Disease [PD]. Through the careful comparison of the genetic material (deoxyribonucleic acid, DNA) inherited by family members who develop PD and those who do not, researchers have been able to identify three genes which are important in PD. Changes in the DNA sequence of any of these three genes, α-synuclein (PARK1), parkin (PARK2) and DJ-1(PARK 7), can result in PD. Most individuals with an altered DNA sequence in these genes will develop PD at an earlier age. Since most people develop PD at an older age, only a small number of with PD have a mutation, or DNA sequence change, in one of these three genes.

The search for genes that increase or decrease the risk for PD is an important area of scientific research. It is hoped that through the identification of these genes, researchers will be able to develop drugs that can counteract the negative effects of these genes. Some researchers are pursuing alternate approaches to develop treatments that might delay or improve the symptoms of PD. Some have attempted to use stem cell research. This is a very different type of research from that which seeks to identify genes that increase the risk of PD. The goal of stem cell research is to potentially replace the cells in the brain that have been altered and died. The promise of stem cell replacement as a treatment for PD is likely to be decades away.

Some researchers are pursuing alternate approaches to develop treatments that might delay or improve the symptoms of PD.

Unfortunately, the media has called the search for genes and the use of stem cells as 'genetic research'. Some have used the terms stem cell research and cloning interchangeably. Few, if any, researchers have proposed to clone individuals as a means of treatment for PD. We must wait to see whether stem cell research will prove a useful therapy in PD. In the meantime, the identification of genes has been an immediate focus for many researchers who hope that this might more rapidly lead to better treatments for PD.

Ten Common Symptoms of PD

If you recognize several of these warning signs in yourself or a loved one, the PROGENI staff recommends consulting a physician.

1. Tremor
2. Rigidity
3. Bradykinesia (slow movement)
4. Postural instability
5. Shuffling Gait
6. Depression
7. Reduced facial expression
8. Change in handwriting
9. Speech changes
10. Personality change

What is a Clinical Trial?

By Kathleen K. Miller, C.O., Indiana University

Before a new drug is made widely available to treat patients with a disease, it must undergo a lengthy process to determine whether or not the drug is safe, what doses of the drug should be used and what kinds of side effects should be expected. A series of steps are usually followed in order to learn this information in a way that is safe and limits the risks to patients.

The steps are typically called Phases. In the first stage, **Phase I**, a drug is given to a small group of healthy people (typically 20 to 80) for the very first time, to determine and establish safety and tolerance of the drug in humans. In **Phase II**, the drug is given to a larger group (typically 100 to 200) of individuals with the disease, to further determine an appropriate range of doses and to learn more about the drug safety and also drug effectiveness. In **Phase III**, the clinical trial tries to expand on the effectiveness and safety of what is known regarding the drug along with selected dosing amounts of the drug (i.e. number of tablets per day or milligrams given to the subject). Sometimes the study protocol is further analyzed to understand the effects of sex, race, ethnic background, age or other indicators on drug effectiveness. **Phase IV** trials are any studies done after a drug is approved. This involves a very large group (typically thousands) of subjects to continue to monitor safety in larger, broader, populations.

What Parkinson's Has Given Me

A man in Texas contacted us after reading our recent PROGENI newsletter and wanted to share his perspective about living with Parkinson 's disease.

My older brother, a first cousin and I participated in the PROGENI study in order to altruistically do what we could to help find answers to our common problem - Parkinson's Disease. We have a long family history of PD and believe God has allowed this, in part, to offer some encouragement to others who struggle with its symptoms.

Diagnosed at age 61, I had experienced tremors on my right side. This was a wake up call. Referring to your last issue of "The PROGENI News", your writers emphasized the need to continue physical exercise. This is just what my primary care doctor, Jim Anagnostis and my Neurologist, Richard Dewey have repeatedly stressed to me.

The tremors, slow movement, and posture issues common to PD patients frustrated me. Currently I am involved in an "Open Label" phase of a clinical trial for a non-FDA approved medication. Throughout this clinical trial and my continued struggle with PD, I have tried to maintain some level of physical exercise; swimming 15 to 20 laps as often as twice weekly, playing tennis and golf. Through the competition I have been humbled by the amount of support and empathy I have received from those with whom I compete. I have come to believe that God has allowed me to become a positive example to others who struggle with set backs. He has done this for me through some affirming results in order to encourage me and others. Over the summer, my wife and I won a local tennis tournament together. While not able to compete at the same levels, He has given me the pleasure of competing at some level.

Another example of this is in golf. Our local golf club sponsored a tournament which had thirty five teams entered. Of those thirty five teams, the one that won the tournament would be invited to play in an International Tournament. Well, I was thrilled to be asked to participate in a four-man team in this qualifying tournament. My team won the local tournament and we were invited to play at the International tournament in North Carolina against 85 teams around from around the world. After three days we finished 40th, about 10 strokes behind.

I wanted to share this experience to make it known that PD patients can succeed and, despite setbacks, life does not have to stop! I wanted also to share my belief that exercise can bring joy to both individuals with and without PD. There are days when I am sad or frustrated, but the support I have received from others has been gratifying. Regardless of whether I win or lose what I know deep down is that God has given me the opportunity to compete in spite of having physical obstacles.

Seeing rewards, other than my efforts in sports, is the feedback I get from my physicians who are involved with my treatment routine. At the completion of my quarterly PD check up and through all of my usual routines which test dexterity and flexibility, my "scores" had improved by 50%; a direct result (I believe) of the exercise routine. I am happy to share the improvements in my "scores" with physicians, family members, and now others with PD. This newsletter serves as a source of encouragement to me because I can read the experiences of others who have PD. Learning to accept PD and learning how to live through PD, is giving testimony to God's grace. I am using this opportunity to share with others what individuals with Parkinson's can do!

Deep Brain Stimulation in PD

With Permission from Michael Rezak, M.D., PhD. M. (2003, Summer). The role of deep brain stimulation. Young Parkinson's Newsletter. American Parkinson Disease Association, Inc.

Deep brain stimulation (DBS) was approved by the FDA in January, 2002 for the treatment of Parkinson's Disease. DBS is a technique that uses a lead or a probe with four electrodes that is implanted in one of two sites within the basal ganglia. The basal ganglia are a group of brain structures that are interconnected and form a "circuit" that allows for smooth voluntary body movement. This circuit is important for individuals with Parkinson's Disease (PD) because it is the area that is affected by the loss of dopamine from the degeneration of one of the components called the substantia nigra. The lead can be implanted in either the internal segment of the globus pallidus or another structure called the subthalamic nucleuses, which are known to be abnormally hyperactive and inhibit normal movement in PD. By applying electrical current to these structures in the brain, doctors are causing the cells in this region to stop functioning and therefore be removed from the basal ganglia circuit. By using these electrodes to stimulate this area, a reversible lesion is made in the structures. If the stimulation is turned off or the DBS is removed, these regions of the brain will return to their original condition and symptoms will return.

DBS requires a team approach generally involving a neurosurgeon, a movement disorders neurologist, a nurse specialist, and a neurophysiologist. The neurosurgeon identifies the target area by using a recent CAT or MRI scan of the patient. The neurophysiologist maps the target area electrophysiologically in order to confirm that the scans are correct. The neurologist will document pre-operative and post-operative motor functions and once the lead is placed in the brain the neurologist will turn the stimulator on to rule out any side effects like numbness, tingling, or muscle twitches. The nurse specialist is highly involved in pre and post-operative testing and documentation.

One month after surgery the nurse and neurologist will start programming the DBS device so the patient will have optimal benefit. Certain parts of this procedure require the patient to be awake so accurate information can be obtained during testing. Anesthesia can be used for all parts of the surgery. Depending on the patient and their symptoms the DBS can be implanted on both sides of the brain in one session or in multiple sessions.

DBS should be considered when symptoms of PD have reached the point where medications are no longer helpful in providing relief or when the dose of medication causes significant side effects. DBS is often used to reduce or eliminate motor fluctuations and drug-induced dyskinesias. Most patients using DBS see their functioning level increase without motor fluctuations or dyskinesias. DBS may also improve gait and balance.

DBS will not be beneficial if PD medications have not benefited the patient or if the patient has been diagnosed with another Parkinsonian syndrome. DBS will not benefit non-motor features of PD like cognitive impairment, mood changes, or changes in blood pressure, bowel, or bladder dysfunction. Dementia is an exclusionary criterion for the DBS procedure since accurate feedback is needed from the patient. In fact, worsening of dementia is a possibility with surgery.

All surgical procedures carry risk. The DBS carries a one to two percent risk of a stroke or hemorrhage which can occur during the operation. Other risks include infection, wire breakage, and skin erosion over the wire. The battery needs to be replaced every three to five years.

According to Dr. Rezak, since 1998, over 100 DBS procedures have been performed at his facility. All PD patients have obtained measurable benefit over their baseline motor functioning which has persisted for up to five years. Most of his patients with DBS implants have significantly reduced their medication dosages and some patients have been able to totally discontinue their medications. If a patient is considering DBS surgery they should select a Center that performs this procedure on a regular basis with an established permanent team.

Dr. Rezak is the Medical Director of the APDA Young-Onset Information and Referral Center and the Director of the Movement Disorders Center and the Functional Neurosurgery Program at Glenbrook Hospital (Evanston/Northwester Healthcare) in Glenview, IL.

PROGENI Researchers at Cincinnati Children's Hospital Medical Center

By Tatiana Foroud, PhD
Indiana University

In each issue of the PROGENI newsletter, we hope to introduce our families to the many PROGENI scientists who through both individual and collaborative research are making a difference in the lives of those with Parkinson's disease. An important part of the PROGENI study is the DNA analysis that is performed at Cincinnati Children's Hospital Medical Center. **Dr. William Nichols** heads the laboratory performing all of these analyses. Dr. Nichols graduated from Indiana University with his doctoral degree in 1989. He then spent nine years at the University of Michigan. Since 1998, he has been in the Division of Human Genetics at Cincinnati Children's, where he has been working on the PROGENI study.

Dr. William Nichols and Liz Byder

Lisa Byder, a research assistant, performs all the experiments and works in tandem with Dr. Nichols on Parkinson's research. Together, they are completing important studies that have allowed us to identify changes in the DNA sequence of the parkin gene and localize a possible gene important in PD risk on chromosome 2.

Using very modern equipment, they are able to carefully analyze stretches of DNA sequence allowing them to identify small sequence changes that may increase the risk that an individual will develop PD. In the next five years, Dr. Nichols will be expanding his efforts on the PROGENI project so that we can rapidly identify additional genes important in PD.

New Faces

We would like to take this opportunity to welcome three new members of the PROGENI team. **Elizabeth Riley** will be working with sites and families to plan autopsies for interested subjects. She has previous experience working in the Pathology Department and the Alzheimer Center here at Indiana University (IU). **Jessie Leatherland** who was the Autopsy Coordinator is now working in the National Cell Repository for Alzheimer's disease, also located here at IU.

Kathleen Miller and Elizabeth Riley

Kathleen Miller will be working on the Progeni Cares study which will be an adjunct to the PROGENI study. (You will be hearing more about this soon!) Kathleen will be working with subjects with Parkinson's disease and an unaffected control. She has been with the IU School of Medicine for 23 years and has been involved in eye movement research and patient care. **Robert Bowman** is a genetic counseling student in the Department of Medical and Molecular Genetics, who will be helping out in the offices of PROGENI.

Did you know?

• **Bob Hope** and his wife Delores have been involved with the National Parkinson Foundation for over 45 years. They have given their time, talent and generosity for the benefit of Parkinsonians throughout the world.

The Bob Hope Parkinson's Research Institute was created because of their generosity. To honor and pay tribute to the late Bob Hope and his wife, the street on which it has stood for over four decades was renamed "Bob Hope Road".

Winter Season and Exercise

By Kathleen K. Miller, C.O., Indiana University

Winter is approaching and with it colder weather which may limit our ability to get out and about. Snow and ice can make it treacherous to keep up daily walking and other forms of outdoor exercise routines. Exercise is still an important aspect in the well being for patients with Parkinson's disease. An excellent alternative form of exercise during inclement weather is aquatic exercises. Water exercising is encouraged because it has a much lower impact on joints. No impact Yoga is another wonderful form of exercise, not only for stretching and flexibility, but also for depression which may be associated with PD.. Many local support groups can provide information about winter time exercise programs. For example the National Parkinson Disease Associations offers an educational booklet on Aquatic exercise for patient's with Parkinson's disease. Single copies may be obtained free of charge by writing to the national APDA office or by calling the toll free number 1-800-223-2732 or Fax 1-718-981-4399.

Before beginning any new exercise program, it is best to contact your local healthcare provider to for help in determining what the best regiment would be for you.

And remember:

- Never over exert yourself!
- Stop and rest when appropriate.
- Listen to your own body.
- Never swim alone

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

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
http://www.parkinsonsaction.org
Tel: 800-850-4726 or 202-842-4101
Calif:707-544-1994 • Fax: 202-842-4105

PROGENI
Department of Medical and Molecular Genetics
975 West Walnut Street
Suite 130
Indianapolis, IN 46202-5251