

What is PROGENI?

Parkinson's **R**esearch: **T**he **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 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

Volume 4 • Summer 2004

Finding Genes That Determine When PD Symptoms Begin

By Nathan Pankratz, Ph.D., Indiana University

The PROGENI study recently published a paper in *Neurology* investigating whether there were genes that helped determine the age at which an individual developed Parkinson disease (PD). For some patients with PD, it is difficult to



If scientists can determine why some individuals begin showing symptoms of PD earlier than others, then it may be possible to find a way to delay the onset of disease symptoms.

identify exactly when they first noticed symptoms of their PD. Others with PD can point to a specific incident or time when they first noticed a shaking in their hand, or problems with their balance as the start of their PD. Although most patients first start showing symptoms around age 60, the age when disease begins (often called age of onset) varies widely, with some patients beginning to show symptoms during adolescence and others not noticing symptoms until well into their nineties. Even within our own PROGENI study, individuals in the same

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family have reported developing PD at quite different ages, sometimes differing by more than 30 years. If scientists can determine why some individuals begin showing symptoms of PD earlier than others, then it may be possible to find a way to delay the onset of disease symptoms.

Trying to identify genes contributing to age of symptom onset rather than to the cause of the disease itself is a relatively new area

of scientific study. The first genes found to cause PD were identified by focusing on those families with early onset of the disease, either childhood or early adulthood. In our study, we have instead used all of the PROGENI families, even though they have a wide range of ages at which PD symptoms began (range: 18-87 years).

The article in *Neurology* provided evidence that there are several genes (on chromosomes 1, 2 and 8) that might affect when someone will develop the disease. The actual genes have not been identified yet, but we have narrowed the part of the chromosomes involved.

To use a common analogy, we are like the FBI trying to track down a criminal. Using the data we have available, we have tracked this person to a specific city. The next step is to identify the neighborhood and then the street, before we go from house to house looking for the individual.

To complete the analogy, once the region on one of these chromosomes is narrow enough, we can check all the genes in the region to see

if there are any changes in the DNA sequence (mutation) that determine when an individual will develop symptoms of PD.

We are hopeful that in the next few years we will learn more about why an individual develops symptoms of PD at a certain age. In the meantime, it is important that we continue to identify families having two or more siblings with PD and try to estimate, as best we can, when these individuals first began to show symptoms.

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Clinical Trials Coordination Center PROGENI Project Team

Investigators and staff at the University of Rochester have played a key role in the PROGENI study for the past 5 years. Led by **Dr. Alice Rudolph**, they helped launch the study by coordinating the efforts of the Parkinson Study Group. The Clinical Trials Coordination Center (CTCC) Project Team includes Elaine Julian-Baros, Jonette Winterkorn, Sue Henderson, Sue Daigneault, Susan Bennett, Tori Ross, and Alice Rudolph.

Elaine Julian-Baros is an Associate Project Coordinator who oversees the collection of regulatory documents from the PROGENI sites. These documents include each site's Institutional Review Board (IRB) approval to conduct PROGENI and a copy of the informed consent form and HIPAA authorization that the IRB has approved for this study.

Jonette Winterkorn is the Senior Staff Accountant who processes quarterly payments to sites for the work that they complete in PROGENI. She knows to pay a site when the Coordination Center receives all those data forms that the Site Coordinator and Investigator completed during your visit!

Sue Henderson is the Secretary who keeps the sites stocked with data forms as they are needed. Sue also types any correspondence to sites that may be needed.

Sue Daigneault serves as the Data Control Clerk and is responsible for keeping track of all the data forms that sites complete and send to the Coordination Center for entry to the database. When the data forms first arrive at the Coordination Center, Sue makes sure that all the pages are received and that the forms are properly labeled. Next Sue records in a special computer program that each of the forms has been received, and prepares them to be sent for key punching.

When the forms are returned, she logs them back in the computer and files each subject's forms in a separate folder that she has created.



Front left to right: Alice Rudolph / Susan Henderson / Elaine Julian Baros / Susan Daigneault / Jonette Winterkorn
Rear left to right: Tori Ross / Susan Bennett

As the Senior Information Analyst for PROGENI, **Sue Bennett** is responsible for answering site questions on the proper way to complete data forms. Sue has final responsibility for ensuring that the data collected on the forms is complete and that the answers are acceptable according to the study protocol. Sue notifies Site Coordinators when forms that are expected haven't arrived at the Coordination Center and when answers are questionable for some reason.

Tori Ross is the Database Manager for PROGENI. She is responsible for creating the computer database structure and for programming the electronic checks that repeatedly review the data for completeness and correctness. Tori is also responsible for periodically transferring the database to Indiana University so that staff there can continue to analyze the data as the study progresses.

In her role as the Co-Principal Investigator for the Coordination Center component of PROGENI, **Alice Rudolph** is responsible for overseeing the study team at the Coordination Center. At the request of the PROGENI Project Coordinator at Indiana University, Alice handles any special issues that may arise with the Parkinson Study Group sites at which PROGENI subjects are seen.

Rotigotine Delivered as a Skin Patch for Controlling Early Parkinson's

The Parkinson's Study group recently published the results of their study of the dopamine agonist, Rotigotine, which is delivered in the form of a skin patch. This paper appeared in the *Archives of Neurology* (Vol. 60 Dec. 2003). There has been a great deal of interest in the results of this study, so we have asked **Dr. Karen Blindauer**, from the Medical College of Wisconsin, who was the co-principal author of the study to explain this study.

Q How can I become a part of the study?

A The study has been completed and no new patients are being enrolled.

Q Is the patch approved by the Food and Drug Administration?

A No.

Q Who are the makers of Rotigotine?

A Schwarz Pharma is the company that makes the drug.

Q What was the conclusion of the study?

A Rotigotine can be safely administered once daily as a skin patch. It was found to improve Parkinsonian signs in patients with early PD.

Q Was this drug compared to existing drugs that are taken orally?

A No, the study only looked at the safety and effectiveness of Rotigotine. However, the study showed that Rotigotine had similar results to that of two other oral dopamine agonists based on a traditional Parkinson's scoring system.

Q How was the study designed?

A The study enrolled 225 volunteers drawn from 36 participating Parkinson Study Group centers. There were five groups each with 45 volunteers. Four groups received different doses of Rotigotine and one group received a placebo for 11 weeks. Rotigotine was delivered through a silicon-based transdermal patch that was replaced every 24 hours.

Q What is the logical next step for making Rotigotine available to patients?

A Traditionally, study findings have to be repeated by an independent research group. We do not have any information of Schwarz Pharma plans on doing further studies or if they have any information on if and when the FDA would approve the drug.

Q Can the patch be used for essential tremor or restless legs?

A To the best of our knowledge, the Rotigotine patch has only been tested in Parkinson's disease. Therefore we have no basis to know if the patch would be helpful for the treatment of other conditions.

Q Where can I get a copy of the actual study?

A You can go to www.archneurolog.com and search their Dec. 2003 issue.

Q Where can I learn more about other clinical trials for Parkinson's disease?

A www.clinicaltrials.gov.

Q Where can I get more information about the Parkinson Study Group?

A Please see the Parkinson Study Group (PSG) website at www.parkinson-study-group.org.

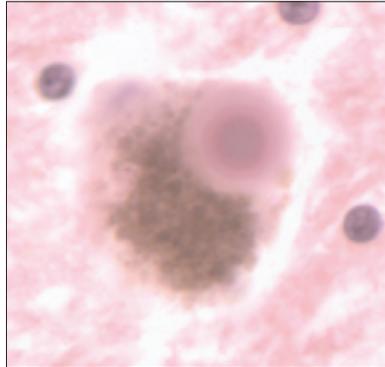
The new **PROGENI website**, <http://progeni.iu.edu>, is an online information center for anyone seeking information on the Parkinson's Research Organized Genetics Initiative.

The site has information for families wanting to get involved with the project, PROGENI publications, links to related sites, and general information on Parkinson's Disease and information on how to contact PROGENI staff.

The Brain and Parkinson's Disease

By Tatiana Foroud, Ph.D.
and Bernardino Ghetti, M.D

During the past decade, a great deal has been learned about the changes that typically occur in the brain of an individual who has Parkinson's disease. Most of the changes can only be observed by careful examination of the brain after death.



Lewy bodies

One of the most typical findings in the brain of an individual with Parkinson's disease is cell loss due to the death of the cells in a particular part of the brain called the substantia nigra. As more cells from the substantia nigra die, the symptoms of Parkinson's disease become progressively worse. Normally, the cells of the substantia nigra make a chemical called dopamine. When these cells die, dopamine levels decrease. The lowered levels of dopamine then cause some of the symptoms of Parkinson's disease.

Individuals with Parkinson's disease typically have other changes in their substantia nigra. These include the presence of Lewy bodies in the cells that remain (See picture in this article). Lewy bodies were first described in 1912 by the pathologist Dr. Friederich Lewy. Recently, scientists have learned that the main protein contained in the Lewy body is alpha synuclein.

A gene called SNCA1 encodes the protein called alpha synuclein. Six years ago, changes in the DNA sequence of the SNCA1 gene were found to cause some rare forms of Parkinson's disease.

Neuropathologists who examine brain tissue carefully test where in the brain Lewy bodies are located. In Parkinson's disease, the Lewy bodies are found not only in the

substantia nigra but also in other cells of the brain stem. In other diseases that may have some symptoms similar to Parkinson's disease, such as Diffuse Lewy Body Disease, the Lewy bodies will be found in the cerebral cortex.

The PROGENI study has encouraged participants to consider examination of the brain at death. Through careful study, neuropathologists can definitively diagnose Parkinson's disease if they observe the expected changes in the brain. The neuropathologist may in some instances learn that the individual did not have PD but instead had another condition, related to Parkinson's disease. This can be important knowledge for the family. **If you are interested in learning more about autopsy, please contact Cheryl Halter at 1-888-830-6299.**

How to Stay Young

Source: American Parkinson's Disease Association

- Throw out non-essential numbers. This includes age, weight and height. Let the doctor worry about them.
- Keep only cheerful friends. The grouches pull you down.
- Keep learning. Learn more about the computer, crafts, gardening, whatever. Never let the brain idle.
- Enjoy the simple things.
- Laugh often, long and loud. Laugh until you gasp for breath.
- The tears happen. Endure, grieve, and move on. The only person who is with us our entire life, is ourselves. Be alive while you are alive.
- Surround yourself with what you love, whether it's family, pets, keepsakes, music, plants, hobbies, whatever.
- Cherish your health: if it is good, preserve it. If it is unstable, improve it. If it is beyond what you can improve, get help and seek knowledge.
- Don't take guilt trips. Take a trip to the mall, to the next country, to a foreign country, but not to where the guilt is.
- Tell the people you love that you love them, at every opportunity.

And always remember: Life is not measured by the number of breaths we take, but by the moments that take our breath away.



Summer Season

Summer is here and it is time to get outside to enjoy this beautiful weather. Exercising can be as easy as finding something that you enjoy doing and incorporating into your everyday routine. Gardening, walking and swimming are all great forms of exercise and enjoyable. When swimming, make sure that you are accompanied by a good swimmer to avoid any problems you may have from Parkinson's, such as freezing or cramping. Always remember to stretch before and after you exercise. Stretching warms the muscles, helps prevent stiffness, and improves balance and flexibility.

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
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