

What is PROGENI?

Parkinson's Research: The Organized Genetics 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 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)**

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PROGENI News

NEWSLETTER FOR PARKINSON'S RESEARCH:
THE ORGANIZED GENETICS INITIATIVE

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PROGENI: Parkinson's Research: The Organized Genetics Initiative

By Tatiana Foroud, Ph.D. - Indiana University



The goal of the PROGENI study is to identify the genes that contribute to Parkinson's disease. To accomplish this goal, we have been recruiting families with at least two siblings (sisters and/or brothers) believed to have Parkinson's disease. This effort has been coordinated at Indiana University School of Medicine. However, the neurologists who are part of the Parkinson's Study Group (PSG), a network of movement disorder specialists located throughout North America, have recruited most families enrolled in this project.

Approximately 450 families have participated in this important National Institute of Health (NIH) funded study. As a result of the active involvement of families we have already begun to better understand why some individuals develop Parkinson's disease. Previously, researchers had identified a gene, called *parkin*, which was abnormal, or mutated, in many individuals with juvenile onset Parkinson's disease. This is a very rare form of Parkinson's disease, in which affected individuals begin to show signs and symptoms of disease in their late teens or early 20s. Japanese researchers reported the first cases. Subsequently, researchers in the PROGENI study have also begun to examine the *parkin* gene and we find that there may be changes in the *parkin* gene even among individuals who develop Parkinson's disease in adulthood. We are currently performing more studies of the *parkin* gene to better understand the types of changes

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The PROGENI Team

When you contact PROGENI, you most likely will reach **Cheryl A. Halter**, M.S. or **Jessica (Jessie) Leatherland**. Cheryl is the Clinical Research Coordinator for PROGENI. She has been with the project from its inception. Cheryl joined the Department of Medical and Molecular Genetics in February 1990 with a B.S. in Psychology and a M.S. in Rehabilitation Psychology from Purdue University. Her background has been invaluable for interacting with families who are coping with a devastating disease such as Parkinson's disease. Her responsibilities with PROGENI include recruiting new families, talking with participants about their disease symptoms, coordinating Study Visits, gathering blood samples, updating families about advances in the project, and maintaining the databases that make this project work. She also maintains regular contact with the doctors and nurses at the 60 PSG sites throughout North America who are taking part in the study.



Cheryl A. Halter (left) and Jessie Leatherland (right)

who are interested in autopsy. Additionally, she works behind the scenes, gathering documents from the PSG investigators that are needed for this National Institutes of Health supported study.

The PROGENI team also includes Nathan Pankratz, a graduate student in the Department of Medical and Molecular Genetics, who is involved in data analysis. P. Michael Conneally, Ph.D. is a Distinguished Professor of Medical and Molecular Genetics and Neurology who has extensive expertise in the study of neurological disorders. Tatiana Foroud, Ph.D. is the Principal Investigator of the study and has overall responsibility for the project.



The PROGENI TEAM: The PROGENI team: From left to right. Back row: Nathan Pankratz, Cheryl Halter, MS. Front row: Jessie Leatherland, P. Michael Conneally, Ph.D., Tatiana Foroud, Ph.D.

Jessie joined the PROGENI team in June 2002. She graduated from Indiana University in May 2002 with a bachelor's degree in biochemistry. Jessie's role in the PROGENI study has several components, with the most important being the development of an autopsy program. She is working with family members to plan autopsies for their loved one's and will play an invaluable role in assisting families

Did You Know?

- Parkinson disease (PD) is a chronic neurological condition named after Dr. James Parkinson, a London physician who was the first to describe the syndrome in 1817.
- According to the National Institute of Neurological Disorders and Stroke, about 50,000 Americans are diagnosed with Parkinson's disease each year, with more than half a million Americans affected at any one time.
- Parkinson's disease affects men and women in almost equal numbers and it has no social, economic, or geographic boundaries.

Why Junk Might Be Bad For Parkinson's Disease

By Eric Siemers, M.D.

Reprinted with permission from the Parkinson's Awareness Association of Central Indiana (PAACI) Newsletter

Most scientific breakthroughs are reported in the medical literature after thorough "peer review" and usually several months of waiting. More immediate gratification can be provided by press releases, albeit without the rigor of scientific peer review. A press release on

August 2, 2002 from a company known as Cephalon provides just this sort of interest. In this communication they describe the initiation of a study of 800 patients with Parkinson's disease using a novel type of treatment known as CEP-1347. The study, implemented by the Parkinson Study Group, will determine if CEP-1347 at any one of three doses slows the progression of Parkinson's disease. Each subject in the study will receive either CEP-1347 or a placebo for two years.

In addition to neurological examinations, each subject will undergo two single photon emission tomography (SPECT) scans at New Haven, Connecticut. By determining the rate of change in the neurological examination, and determining the rate of loss of dopamine cells using the SPECT scans, the effect of CEP-1347 on the rate of Parkinson's disease progression will be assessed. The subjects enrolled in this study will have early, mild PD that does not require treatment with Sinemet or several other drugs. Given the fact that 800 subjects will be enrolled and followed for two years, results from this study are not likely to be available for at least 3 years.



Eric Siemers, M.D.

A study of 800 patients treated for two years requires a great deal of effort by the subjects enrolled, investigators, employees of Cephalon and employees of the FDA. The magnitude of this effort would suggest that marked effects of CEP-1347 might be expected in PD. The possible effects of CEP-1347 in PD are based on the current understanding of complex changes that occur in cells that become sickened by any one of several insults, and will ultimately die.

Although the ultimate cause of PD of course is not yet known, what is known is that a variety of markers for cell death are found in the brains of patients dying with PD. One of these markers is a protein known as *c-jun*. Another protein known as *c-jun N terminal kinase* activates *c-jun* so that it can cause changes in expression of the cell's DNA, which in turn lead to cell death. *c-jun N terminal kinase* fortunately has been abbreviated as *jnk* (pronounced "junk"). The thought is that a drug that inhibits *jnk* might slow the rate of cell death. In other words, one might say that taking out your *jnk* is a particularly good idea for patients with PD! Despite the complexities of the biochemistry, the important conclusion is that molecules that inhibit *jnk* activity or the activity of other related proteins could act to slow the rate of cell loss in PD.

Evidence from animal models does exist to suggest that treatment with a *jnk* inhibitor such as CEP-1347

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10 Common Symptoms of PD

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

- If you recognize several of these warning signs in yourself or a loved one, the PROGENI staff recommends consulting a physician. Early diagnosis is an important step in getting appropriate care and support services.

Parkinson Research

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that might occur and to find ways to determine who is most likely to have an abnormality in this gene.

Another important part of the PROGENI study is to identify new genes that increase the risk an individual might develop Parkinson's disease. During the past four years, we have been working on this question and have recently published a paper that suggests that there may be at least two genes, one on chromosome 2 and the other on the X chromosome, that might increase the risk an individual develops Parkinson's disease. These are very early studies and we still do not know what these genes might be. However, we feel it is important that we have taken this first step toward answering this important question.

We always keep in contact with families who have participated in our study. It is important that we learn about new family members that may be showing signs of Parkinson's disease so that we can ask them if they would like to participate in this important research project. We look forward to keeping you informed of the important scientific information we are learning from this study. We also want to thank you again for your willingness to help us better understand the genetics of Parkinson's disease.

Recent PROGENI Scientific Publications

William C. Nichols, Nathan Pankratz, Sean K. Uniacke, Michael W. Pauciulo, Cheryl Halter, Alice Rudolph, P. Michael Conneally, Tatiana Foroud and the Parkinson Study Group. Linkage stratification and mutation analysis at the parkin locus identifies mutation positive, Parkinson disease families. *Journal of Medical Genetics*, 39:489-492, 2002.

Nathan Pankratz, William C. Nichols, Sean K. Uniacke, Cheryl Halter, Alice Rudolph, Cliff Shults, P. Michael Conneally, Tatiana Foroud, and the Parkinson Study Group. Genome screen to identify susceptibility genes for Parkinson Disease in a sample without parkin mutations. *American Journal of Human Genetics*, 71:124-135, 2002.

Why Junk Might Be Bad

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might slow the rate of progression of PD. In standard animal models of PD using the toxin MPTP, CEP-1347 has been shown to decrease the number of dopamine cells lost. Treatment with CEP-1347 does not cause an increase in dopamine cells or the amount of dopamine in the brains of these animals, but the amount of cell loss after exposure to MPTP is attenuated. This type of data would suggest that a patient treated with a *jnk* inhibitor might benefit from a slowing of the gradual worsening that is unfortunately inevitable with PD. Treatment with this type of compound would not be expected to cause an actual improvement, although such improvement could occur.

The potential benefit provided by an experimental drug such as CEP-1347 must be weighed against the potential toxicity. One of the luxuries of communication by press release is that the degree of enthusiasm can be relatively unfettered, and in the press release from Cephalon potential side effects of CEP-1347 were not discussed. But to perform a study of 800 patients treated for two years with an investigational drug, the FDA requires extensive animal testing to assess safety. Additionally, studies of small numbers of healthy volunteers and perhaps small numbers of Parkinson's patients almost certainly have been done. Before participating in any research study, a subject is required to read and sign an "Informed Consent Statement." In this document, the potential risks and benefits of an experimental treatment are described in language that can be understood by patients and their families. The decision to participate in any research study should be based on an understanding of these potential risks and benefits.

In the case of CEP-1347, a very large, lengthy and demanding study has been initiated that will require the efforts of 800 patients, scores of investigators and an investment on the order of \$30 million by Cephalon. Historically, the chances of a drug being successful at this stage of development are about one in four. While this effort would appear to be an example of high stakes poker, it is only through such efforts that new medications that slow the rate of progression of PD can be discovered.

Dr. Eric Siemers is Clinical Associate Professor of Neurology, Indiana University and Senior Clinical Research Physician at Eli Lilly and Company.

Autopsy: An Important Part of Our Research

By Tatiana Foroud
and Jessie Leatherland

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.

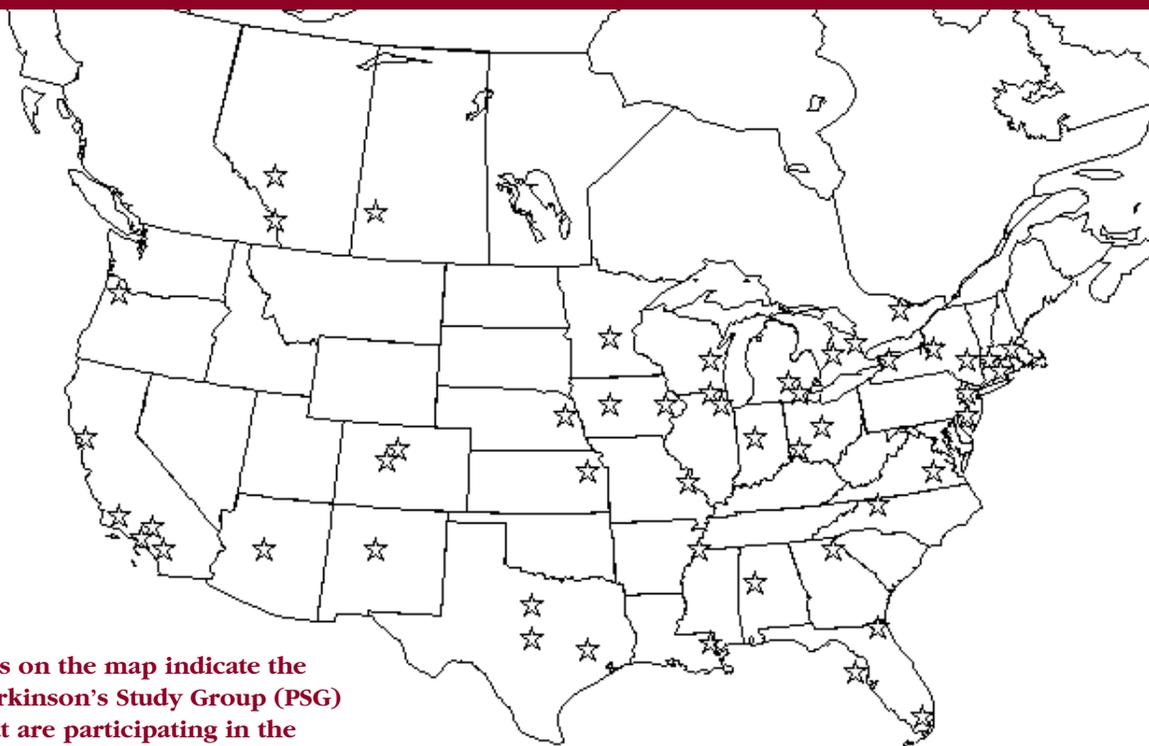
Many families are reluctant to discuss an autopsy and wait until the last moment to do so. The time when a family member passes away is filled with many emotions as well as the need to carry out any arrangements and notify the necessary individuals. By having the autopsy planned well in advance, this 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 Jessie Leatherland at 1-888-830-6299 or 317-278-8413.

PROGENI Sites



☆ The stars on the map indicate the sixty Parkinson's Study Group (PSG) sites that are participating in the PROGENI research study. There are PSG sites located in the United States, Puerto Rico and Canada.

☆ Puerto Rico

Useful Sources for Information and Support

The American Parkinson Disease Association (APDA)

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

The Michael J. Fox Foundation for Parkinson's Research

<http://www.michaeljfox.com>
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)

Fame & Parkinson's Disease

It is always interesting to find out you have something in common with a famous person. You may find it interesting to know that the following people have been diagnosed with Parkinson's disease:

- Jack Backus (the voice of "Mr. Magoo")
- Michael J. Fox
- Pope John Paul II
- Janet Reno
- Muhammad Ali
- Salvador Dali

This list is just a small sample of the many famous people who have been affected with PD. Some of these famous people, such as Michael J. Fox and Muhammad Ali, are very supportive and actively involved in Parkinson's disease research.



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