

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, 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 and the PARK8 Gene

By Tatiana Foroud, Ph.D., Indiana University

In the past few months, a new gene was identified that can cause Parkinson's disease (PD). This gene was initially identified in families from remote regions, like the Basque mountains in Spain. The gene, PARK8, encodes a protein named dardarin by the researchers, from the Basque word dardara, which means tremor, a major symptom of Parkinson's disease. Therefore, it was critical to better understand whether changes in the DNA sequence of this gene might also cause PD in families from North America. The PROGENI study was eager to learn this information and with our large number of families participating in our research study, we were able to quickly address this question.

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Nutrition and PD

By Katherine Ginther, B.S., Indiana University

Nutrition is a very important concern for many people. Eating the right foods in the correct amount, according to the Food Guide Pyramid, is important for everyone to remember. Persons with PD, however, may have additional concerns. It has been shown that diet has an effect on medication taken by PD patients.

Levodopa (Dopar, Larodopa, Madopar, Prolopa, Sydnopa, and Sinemet) and protein (high amounts are found in foods such as meat, eggs, beans, and nuts) compete for digestion in the stomach. Protein is digested and absorbed before the medication,

Doctors recommend that levodopa be taken 30 minutes before eating a meal, in order to ensure adequate digestion.

causing a delay in the digestion and absorption of levodopa into the bloodstream.

There is also a delay in absorption of levodopa from the bloodstream to the brain, since protein is again absorbed first. Because of these delays, levodopa may appear to be less effective in treating PD

at times. Some PD patients find that levodopa “wears off” and movement becomes difficult again after years of continued use. Sometimes the amount of protein a person includes in their diet can be adjusted to prolong the effectiveness of levodopa. Doctors recommend that levodopa be taken 30 minutes before eating a meal, in order to ensure adequate digestion.

Remember that protein is a necessary part of a healthy diet, so it should not be avoided completely. If you feel you need help with your diet, consult a registered dietician.

PROGENI and the PARK8 Gene Continued from page 1

We began our studies by testing a single spot in the DNA sequence of the PARK8 gene. In some families, a change at this particular position of the DNA caused PD. Therefore, we studied the DNA of our PROGENI families and found that in the 358 families that were tested, this particular change in the DNA sequence was found in 20 different families.

Thus, this single mutation caused PD in 5% of the PROGENI families and is now the most frequent mutation identified to date in families with PD. Individuals in the PROGENI study who had this DNA sequence change had typical clinical findings of PD. We have now published these data in the journal *Lancet*. The manuscript is entitled “Genetic screening for a single common LRRK2 mutation in familial Parkinson’s disease.” Once this manuscript was published, it quickly gained world wide recognition and the results from this data are

being noted on web sites across the United States and through out the world, including London, Paris and Beijing.

Thus, this single mutation caused PD in 5% of the PROGENI families and is now the most frequent mutation to date in families with PD.

There is a great deal of work still to be done, including testing the entire PARK8 gene to identify additional changes in the DNA sequence that might cause or contribute to PD. We believe that this is very exciting work and

will be very important data that will be needed to plan future genetic tests that might be used in diagnosing PD. As with all of our research studies, we cannot tell PROGENI participants whether or not they or their family members have a particular DNA change. However, we can share our overall study results with our study families and will continue to publish all of our data results so that PD researchers and physicians can continue to learn more about why individuals develop PD. We hope that our studies will allow more effective treatments for PD to be developed.

Genes That Cause PD

By Nathan Pankratz, Ph.D., Indiana University

It was not long ago that many scientists believed that Parkinson's disease (PD) was solely the result of one's environment. Now, with the recent identification of six genes known to cause PD and a handful of other genes that may increase the risk for PD, scientists are developing a more complete picture of how PD comes about that includes a combination of genetic and environmental factors.

The first PD gene was identified by studying a very large family with PD, where sixty family members had the disease. After searching through their DNA, a mutation or change in the normal DNA sequence was found in the alpha-synuclein gene (also called PARK1) in the affected family members. This gene codes for a protein that is also called alpha synuclein. Individuals with a mutation in the alpha synuclein gene either produce a faulty type of the protein or produce too much of the normal protein, both of which causes the existing protein to stick together and become poisonous to the body. Once this had been learned, scientists quickly studied this gene in other families with PD to determine if they also had a change in the DNA sequence of this gene. However, after testing thousands of families, very few were found to have a mutation in the alpha synuclein gene and most of them were from very distinct geographic regions in Italy, Greece and Germany. Therefore, changes in the DNA sequence of the alpha synuclein gene are likely to be a relatively rare cause of PD. Nevertheless, an incredible amount of information has been learned about PD that would not have been learned this quickly, if at all, had the alpha synuclein gene not been identified.

A year later, the second gene known to cause PD was identified. This gene was called parkin (also known as PARK2). This gene encodes for a protein, which is also called parkin, and is responsible for removing excess proteins from the cell. As we mentioned above, when there is too much alpha-synuclein in the brain it can cause PD, so if the parkin gene is not working correctly, alpha-synuclein and a few other proteins will collect to

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.

dangerous levels, and Parkinson's disease sets in at an early age (frequently as early as the teenage years in these individuals). Mutations in the parkin gene are a more common cause of Parkinson's disease than mutations in the alpha-synuclein gene. Yet, mutations in the parkin gene have been found in fewer than 1% of individuals with PD.

In the past few years, there has been a burst of information about additional genes that appear important in PD etiology. The PARK6, PARK7, and PARK8 genes were identified within about a year from each other (see accompanying article about the PROGENI study and PARK8). With the discovery of the three genes, PD researchers have been trying to understand how changes in the DNA sequence of these genes might cause PD. Researchers believe that each of these genes is important in helping the brain remove unnecessary and unneeded proteins from the brain, a process which acts a bit like the brain's garbage disposal. It appears that among individuals with PD, bad proteins are either collecting too quickly and the brain's garbage disposal system can't keep up with them, or the brain's garbage disposal system is damaged and a normal level of garbage isn't being removed fast enough.

With the identification of each new PD gene, we learn more and more about what has to go wrong in the brain to cause PD. Armed with this new knowledge of what can cause the disease, scientists hope to devise new ways to combat the disease so that future generations will not suffer from PD. In the meantime, it is important that the PROGENI study continue to identify families having two or more siblings with PD.

In this way, we will identify additional genes that can cause PD which we hope will lead to the rapid development of new therapies for treating the disease.

Coordinator's Corner

Getting to Know the PSG Coordinators

Carolyn Peterson, RN Site: Creighton University

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

A We have been working together nine years. We each were involved in research at other places prior to that.

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

We see as many as 15 in a day or 30-40 a week.

Q How many PROGENI Study Visits have you done?

A We have done 18 study visits.

Q What is your favorite part of the Study Visit?

A My favorite part is getting to know all the places people have lived and the jobs that they have had in their life. People are interesting.

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

A Being involved in PROGENI gives people hope that the cause and cure can be found. Patients always want to know "what's new in treatment." It is hopeful for them that we are still looking.

Jean Hall, RN Site: Hotel Dieu Hospital-CHUM

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

A Eight years

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

A Dr Panisset sees about 10 per day, and about 50 per week. I however, tend to see only my study patients and if I have time I will see some of the clinic patients also.

Q How many PROGENI Study Visits have you done?

A 60 study visits, 29 completed families

Q What is your favorite part of the Study Visit?

A I enjoy meeting our clinic patient's affected sibling. Sometimes on a field trip, Dr Panisset and I have met the entire family. It is nice to see these families in their home environments. Some of our patients have led such interesting lives.

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

A Being involved with finding a genetic link to PD which may help future generations.

Michael J. Fox Foundation Awards Grant to the PROGENI Study

By Tatiana Foroud, Ph.D., Indiana University

Since 2000, the Michael J. Fox Foundation for Parkinson's Research (MJFF) has been actively involved in the advancement of Parkinson's disease (PD) research. The MJFF has chosen to focus its efforts in specific areas so as to maximize its impact on PD research and treatment. One of the first areas in which the MJFF chose to focus its research efforts was genetics.

In October 2003, a group of researchers, led by the PROGENI team, were awarded one of five Edmond J. Safra Global Genetics Consortia grants by the MJFF.

The PROGENI investigators have teamed up with a group of international researchers from Europe and the United States to focus our efforts on one particular region on chromosome 5. We chose to focus on this chromosome because all of the studies have found evidence that there may be a gene on chromosome 5 that increases a person's risk to develop Parkinson's disease.

This international, collaborative group will now concentrate its joint efforts on examining chromosome 5 to determine more definitively whether a gene on that

chromosome might be important in Parkinson's disease susceptibility. To accomplish this goal, all of the collaborating researchers will study the same sequences of DNA from all study participants. Then, genetic analyses will be performed to try to determine where on chromosome 5 the group should look to find a gene that could increase a person's risk of developing Parkinson's disease.

We hope that through our joint efforts we will be able to more rapidly identify genes that increase the risk for Parkinson's disease. We look forward to updating you in the future on the results of these analyses!



Parkinson Disease: Impact on Driving

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

Driving represents freedom and control for most people. It also represents an economical importance for many people. Driving is something many of us just do, seemingly without thinking. However, driving requires a complex set of skills, some of which may be affected by Parkinson's disease (PD). The symptoms of PD can make it difficult to react quickly to hazards while driving, turning the steering wheel, using the gas pedal or pushing down the brake pedal.

The decision to give up driving is a difficult one; however the real issue is safety for the driver and others on the road.

When evaluating whether someone is capable of driving safely several factors must be considered.

- Does the person have adequate visual acuity?
- Can they judge the speed of other vehicles in order to keep a safe distance from other vehicles on the road?
- Most importantly, are the person's reflexes fast enough to respond to unexpected situations that may arise while driving?

The decision to give up driving is a difficult one; however the real issue is safety for the driver and others on the road. Often times, family members of those with Parkinson's disease may feel that it is time for the person to stop driving. They may or may not be correct in their judgment of the person's driving ability. It is best to discuss this decision with the physician who is caring for the person with Parkinson's disease. She or he can be very helpful in deciding whether the patient is safe to drive. The physician can offer an objective opinion of the person's ability, both physically and mentally, to handle the complex skills necessary to drive. If there is disagreement within the family, the physician can be the one to make the decision for the family to recommend that his/her patient should no longer drive. Having a third party make this decision may eliminate some of the resentment the patient might have toward their loved ones for questioning their abilities.

Making the decision to stop driving is rarely easy, no matter the circumstance. As we get older or deal with disease, the decision may become more difficult. It may mean reduced independence and require asking others for help or transportation. However, when the decision is made together with family members and physicians, the transition can be less difficult. There are resources available that provide transportation for those that can not drive. Many senior centers, religious organizations and other local service groups often offer transportation services in the community.

For more information on how to find help with transportation call the ElderCare locator at 1-800-677-1116 or the Easter Seals Project ACTION at 1-800-659-6428.

The PROGENI Scientific Steering Committee

By Cliff Shults, M.D.
University of California, San Diego



Cliff Shults, M.D.

to understand the genetics of Parkinson's disease. To help address all issues related to the clinical aspects of Parkinson's disease, the PROGENI study created a Scientific Steering Committee. This committee is led by Dr. Cliff Shults at the University of California, San Diego.

Dr. Shults has been involved in Parkinson's disease research for 23 years and was the principal investigator of the study "Effects

of Coenzyme Q10 in Early Parkinson's Disease", which is commonly referred to by the nickname "QE2." As the leader of the PROGENI Scientific Steering Committee he works with the PSG neurologists and coordinators, the researchers at the Clinical Trials Coordinating Center in Rochester, New York as well as the investigators at Indiana University and Cincinnati Children's Hospital Medical Center. Dr. Shults and the PROGENI Scientific Steering Committee are asked to provide advice on all types of clinical issues related to Parkinson's disease, help in designing and modifying the forms used during the study visit and also review all the papers describing the study's results.

The PROGENI Scientific Steering Committee is made up of a number of PSG neurologists and Parkinson's

disease experts who together have hundreds of years of experience with Parkinson's disease.

The members of the Steering Committee include: P. Michael Conneally, Ph.D., Indiana University School of Medicine, Indianapolis, IN, Kelly Lyons, PhD, Kansas University Medical Center, Kansas City, KS, Karen Marder, MD, Columbia-Presbyterian Medical Center, New York, NY, Frederick Marshall, MD, University of Rochester, Rochester, NY, David Oakes, PhD, University of Rochester, Rochester, NY, Alice Rudolph, PhD, University of Rochester, Rochester, NY, Clifford W. Shults, M.D., University of California, San Diego, San Diego, CA, Aileen Shinaman, JD, University of Rochester, Rochester, NY, Eric Siemers, Eli Lilly & Company, Indianapolis, IN

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