

PROGENI News

NEWSLETTER FOR PARKINSON'S RESEARCH:
THE ORGANIZED GENETICS INITIATIVE

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What is PROGENI?

Parkinson's Research: The **O**rganized **G**enetics 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 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.

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
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(PROGENI)**

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PARKINSON DISEASE AND LRRK2

By Tatiana Foroud, Ph.D., Indiana University

Many PROGENI family members have contacted us to learn more about LRRK2, the most recently identified Parkinson disease (PD) gene. LRRK2 stands for leucine-rich repeat kinase 2 and the gene is located on chromosome 12. It codes for a protein called dardarin. Families have asked us about the possibility of genetic testing for this or other genes.

The LRRK2 gene is a very large gene. It consists of 51 different pieces, called exons. DNA sequence changes in any of these 51 exons could increase the risk for PD.

To determine exactly which DNA sequence changes are important risk factors for PD, PROGENI researchers as well as PD researchers worldwide have been studying the DNA of individuals who have been diagnosed with PD. Equally important have been studies that examine the DNA of individuals who do not show symptoms of PD.

In the accompanying article in this issue of the PROGENI News, we describe how researchers perform the studies that can identify DNA sequence changes

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SEQUENCING OF THE LRRK2 GENE

By Veronika Elsaesser, Diane Marek, and William C. Nichols, Ph.D., Cincinnati Children's Hospital Medical Center

DNA, deoxyribonucleic acid, is the building block of life which contains the coding information specifying all components in organisms and allows for their function. DNA is composed of nucleotides (a deoxyribose sugar, phosphate group, and nitrogen base). There are four different nucleotides which make up the DNA molecule:

adenine, guanine, cytosine, and thymine. Adenine pairs with thymine while cytosine pairs with guanine forming a double helix. A DNA double helix is pictured as a twisted ladder with the base pairs forming the rungs of the ladder. This double stranded helix coils itself into a structure called



From left to right - Mike Pauciulo, Diane Marek, William Nichols, PhD, Veronika Michaels

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Sequencing of the LRRK2 Gene

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a chromosome. In humans there are 23 pairs of chromosome. Each chromosome contains sections of DNA that code for proteins called genes. Humans have approximately 30,000 genes. Genes are made up of introns and exons. The exons are the portions of the genes which actually code for the proteins and the introns are DNA sequences in between the exons. The exons are put together in the correct order without the introns to form what is called messenger RNA, or mRNA. mRNA is then “translated” into a protein made up of amino acids. The sequence of amino acids which was determined by the DNA sequence of the gene specifies the shape and function of the protein. Mutations are the result of a change in one or more nucleotides at the DNA level which results in alteration of the protein sequence. Mutations can thus alter either the protein shape or function resulting in disease.

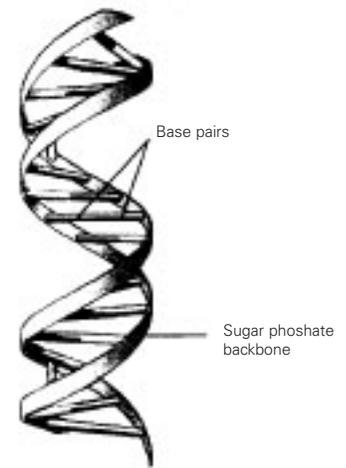
Mutations in LRRK2 cause Parkinson disease (PD) in some individuals. Much is still to be learned about LRRK2. However, having a mutation does not necessarily mean that you will definitely develop PD. Studies are still ongoing to determine one’s chances for developing PD if they carry an LRRK2 mutation.

In the next paragraphs, we will describe how researchers study DNA in order to determine if an individual has a change in their DNA sequence coding for LRRK2.

Sequencing is a tool that researchers use to find some types of mutations in a targeted region of DNA. PCR stands for polymerase chain reaction. This is the first step in the sequencing of a gene. It is the process by which one can obtain many copies of a specific region of a certain gene. This is important to verify that the correct sequence has been copied.

Once this DNA product is verified to be correct, it can be sequenced. Sequencing is the process whereby we determine the order of nucleotides in our gene product. Since we know which nucleotides should be present, and in what order, we can determine whether any are incorrect, thus potentially causing what is known as a mutation.

This is an illustration of DNA



Source: <http://ghr.nlm.nih.gov/info=basic/show/dna>

“Mutations in LRRK2 cause Parkinson disease (PD) in some individuals. Much is still to be learned about LRRK2. However, having a mutation does not necessarily mean that you will definitely develop PD.”

A mutation occurs when the DNA sequence is changed such that it leads to a change in the protein sequence.

Not every DNA sequence change will result in a change in the protein’s sequence or function. This is why not every mutation we find will necessarily result in PD. Sometimes changes in the DNA or protein sequence do not alter the protein’s function and thus this alteration does not cause disease. Individuals have two copies of the LRRK2 gene, one from their mother and one from the father. People who have the same base at the same position on both copies of the gene are referred to as “homozygous”. Individuals who have different DNA sequences on their two copies of the gene are called “heterozygous.”

The End Brings Hope For the Future

By Linda Cooper, PROGENI participant

4-22-05

I sit in the quiet of the Hospice room, my mother dying of the disease that is also robbing me of my independence, clarity of thought and physical abilities. To see her struggle with every breath, muscles paralyzed while her limbs shake uncontrollably seems too cruel a way to die.

I look into the very first set of eyes that met me as I entered this world. The very eyes that have never made me feel a failure or shame but have only encouraged me and loved me. The very same eyes that have seen both her sons laid to rest.

I am planning to donate her brain to study of Parkinson's disease. To discuss the details at this time seem cruel and morbid. Yet we both would stop at nothing to find the cure to this insidious curse. I touch her head and hope that science appreciates the gift that she is giving them

My blessing is she has never known of my diagnosis. I could spare her that

4-23-05 4:45 am

Nurse has woken me up to let me know that her breathing is labored and that she will pass in the next hour or so. How do they know?

I take as many of my clothes off as I can and lie in bed with her...letting my body encompass her and hold her head and let her know it be ok.

“ **Funny thing Parkinson's... even up to the end. The shaking did not stop.** ”

Her breathing is only about two breaths an hour

Funny thing Parkinson's... even up to the end. The shaking did not stop.

I hold her and wait for one minute or two at 6pm her breathing never started. But that is not how I knew she was gone

The shaking finally stopped...

Aside from the embarrassment of her tremor, the unsteadiness, her feeding issues, her cognitive concerns ... her most troublesome symptom of the disease was the very last to exit her body

And Finally...the shaking stopped...

An autopsy is pending on Linda's mother through the PROGENI study.

Please contact the PROGENI staff if you are interested in autopsy for yourself or a family member.

PROGENI at the World Parkinson Congress

By Cheryl Halter, M.S., CCRC
Indiana University

The first World Parkinson Congress was held in Washington DC February 22-26, 2006 and PROGENI was there. The Congress was a unique forum that brought together people with Parkinson disease (PD), their families and caregivers, clinical professionals and investigators researching PD. Michael J. Fox kicked off the Congress which had 3,161 registered participants from over 50 countries. Of these registered participants over 1,800 were medical professionals, and over 1,100 were people with PD and their families.

Over the 5 days, the Congress provided a wide range of information about PD from nearly 270 presenters. Scientific, clinical, spiritual, and practical information was shared. Ranging in size from large, double ballrooms full of people to small intimate workshops, the varied setting of the presentations added to their appeal. Attendees could take part in panel discussions with world renowned leaders in the field, or could share private moments discussing life with PD with other families and caregivers. The Congress also provided scientists who study PD a unique opportunity to interact directly with people living with PD. I heard over and over again, throughout the conference, how exciting it was for professionals and persons with PD to be together at the same event, discussing the same topics and learning about each other.

PROGENI was represented at the Congress by Dr. Tatiana Foroud, Principal Investigator of the study. She presented information about genetic counseling in PD. The topic allowed for lively discussion and was very well received. PROGENI was also represented by a professional poster prepared by Dr. William Nichols, the geneticist performing the molecular analysis for PROGENI. His poster, describing recent finding by the PROGENI study, was one of over 340 posters on display during the conference. PROGENI was also present at the Congress as an exhibitor. Study staff manned a booth in the exhibition hall, distributing study materials and recruiting potential families.



Cheryl Halter, M.S., CCR at the the PROGENI exhibition booth at the first World Congress held in Washington D.C. in February 2006.

Staff also had the opportunity to network with other professionals working with persons with PD. One of the most exciting parts, for me, of the exhibit was having the opportunity to meet many PROGENI participants in person. Without the support of PROGENI family members, PROGENI could not be the success that it is.

The next World Parkinson Congress will be held in Paris France, in June of 2009. Perhaps we will see you there!!

Did You Know?

- PROGENI enrolled its first family in 1998 and currently has collected information from nearly 800 families.
- We have gathered information on subjects from 49 U.S. states, the District of Columbia and Puerto Rico (only Delaware is not represented). Additionally, we have subjects from seven of the ten Canadian Provinces (New Brunswick, Nova Scotia and Prince Edward Island are not represented) .
- We have conducted over 1500 study visits including one in Italy.
- We have collected blood samples from individuals in England, Germany, Israel, India, Ireland, and the Netherlands.

Parkinson Disease and LRRK2

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in a gene. Once a DNA sequence change has been found, researchers must determine whether this change alters the protein that is being coded by this piece of DNA. The production of an altered protein is thought to cause or contribute to the symptoms of PD. It is important to determine whether this particular DNA sequence change is found only in people with PD or if it is also found in people who do not have PD. DNA sequence changes that are found more often in people with PD are more likely to increase the risk for PD than are DNA sequence changes that are found equally in people with and without PD.

Performing these DNA studies, we have learned a great deal about LRRK2 and the risk for PD. There is one particular DNA sequence change, called G2019S, which is found more frequently than any other change in the LRRK2 gene. G2019S means that at position 2,019 of the dardarin protein the amino acid glycine replaces the usual amino acid called serine. Among individuals with PD who also have a family history of the disease, this particular change occurs at a frequency of about 5%. This change occurs at a lower frequency (only 1-2%) among individuals with PD who do not have any other family members with the disease. Individuals with this sequence change typically develop PD in their 50's or 60's. However, researchers have found some individuals who have inherited this

sequence change and who have not yet developed PD even in their 70's. This observation suggests that it is possible that some people who have the G2019S mutation may never develop PD. PROGENI researchers continue to study the LRRK2 gene. We have identified additional DNA sequence changes that occur at higher frequency among individuals with PD as compared with individuals who do not have PD (i.e. healthy controls). Each of these new DNA sequence changes are relatively rare and found in only a few PROGENI family members.

At this time, DNA sequence changes in LRRK2 are still an active area of research. The effects of these changes are not yet fully understood. For this reason, PROGENI researchers, and many other PD researchers, believe that widespread diagnostic screening of the LRRK2 gene is not appropriate at this time. It is important that researchers and physicians understand which DNA sequence changes in the LRRK2 gene can increase the risk for PD. It is also important to know that even if a person with PD has an LRRK2 gene mutation, it is very unlikely that their PD treatment would be altered. Therefore, it is vital that researchers perform the critical studies to better understand LRRK2 before clinical screening for the gene is undertaken. These studies are ongoing and can only continue through the support and involvement of PROGENI families and other persons with PD.

PROGENI and PROGENI Cares Research Continues

Our PROGENI families have provided us many important clues to the genetics of PD. As we have discussed in previous newsletter issues, our 800 families have helped us to better understand the role of the parkin (PARK2) and the leucine-rich repeat kinase 2 (LRRK2, PARK8) gene (Vol. 5 Winter 2005.) In future issues, we will be telling you about research progress in both PROGENI and PROGENI Cares.

The **PROGENI website**, <http://progeni.iu.edu>, is an online information center for anyone seeking more information. 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.

A Guide to Parkinson's Disease Medical Terminology

By Kathleen K. Miller, C.O, CCRP

Below is a list of common medical terms and their meanings which may make your exam visit less confusing and give you a better understanding of the disease:

Akinesia: Inability to move ("freezing") or difficulty in beginning or maintaining a body motion.

Ataxia: A mobility-impairment condition marked by loss of balance and decreased coordination.

Bradykinesia: The slowing down and loss of spontaneous and voluntary movement.

Cogwheeling: A jerky or ratchet-like sensation felt by a physician when a patient's limb is moved around a joint.

Dysarthria: Slurred or otherwise impaired speech.

Dyskinesias: Involuntary, uncontrollable, and often excessive movement. These movements can be lurching, dance-like or jerky, and are distinct from the rhythmic tremor commonly associated with Parkinson's disease. A common side effect of many drugs used to treat Parkinson's disease.

Dysphagia: Difficulty in swallowing.

Dystonia: Abnormal and awkward posture or sustained movements of a hand, foot, or other part of the body; may be accompanied by rigidity and twisting.

Freezing: Abrupt and temporary inability of Parkinson's patients to move that frequently occurs at a boundary such as a door or when exiting a car.

Neurodegenerative: Refers to conditions such as Parkinson's that are characterized by the loss of cells in the central nervous system.

Rigidity: Abnormal stiffness in a limb or other body part. It is most apparent when an examiner moves a patient's limb – as in cogwheeling.

Tremor: Unwanted rhythmic movements (may be fast or slow) that may affect the hands, head, voice or other body parts.

Wearing Off: Loss of effectiveness of Parkinson's medications between doses. If the effectiveness of a medication does not last until the next dose is due, it "wears off".

Sources: *Stedman's Medical Dictionary (26th edition)*

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

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