PROGENI News

Newsletter for Parkinson's Research:
The Organized Genetics Initiative

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APPROACHES TO DISCOVER GENES THAT INCREASE THE RISK FOR PD

By Tatiana Foroud, Ph.D., Indiana University

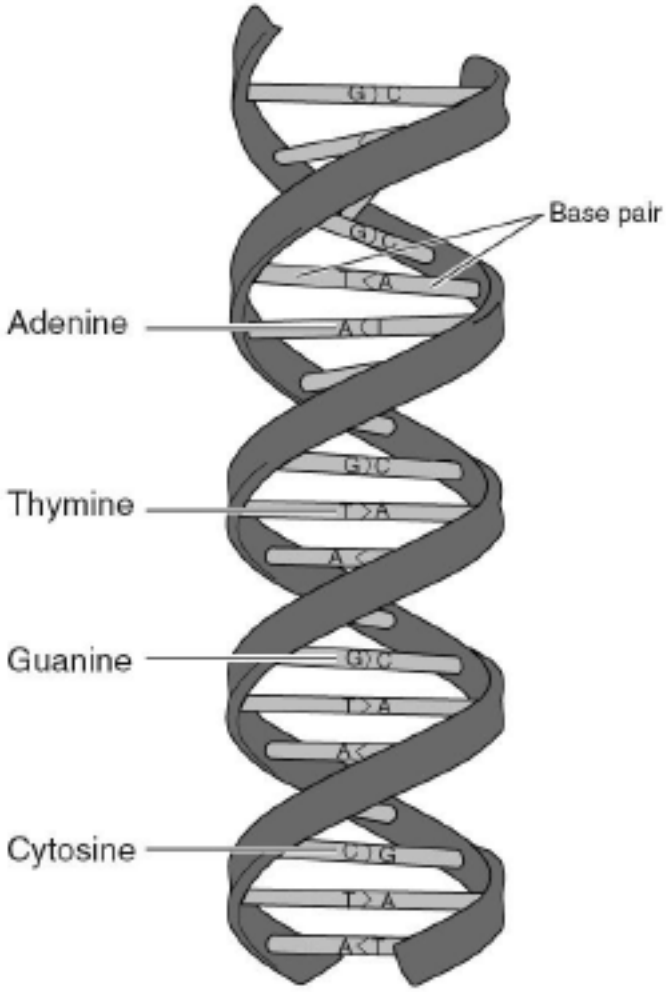
In the past few years, there has been a revolution in the ways that researchers can study DNA, our genetic material. In the past, when we would begin to hunt for genes that increase the risk for Parkinson disease (PD) we would analyze about 400 different positions along an individual's DNA. Today, it is now possible to test hundreds of thousands or in some cases even a million different positions along our DNA.

How are we able to do this?

Let's begin with a review of DNA. Each cell in our body, with a few exceptions, contains deoxyribonucleic acid (DNA), which is the genetic building block. DNA is often depicted as a ladder. The rungs of the ladder are made up of a series of four nucleotides, coded by four different letters: A (adenine), T (thymine), G (guanine), and C (cytosine). The DNA sequence consists of over three billion letters. Within this sequence are particular stretches of DNA, called genes, that determine things such as eye color, hair color, and we believe influence an individual's risk for PD.

Researchers have known about the basic structure of DNA for nearly 50 years. However, we have only slowly been able to develop tools and techniques for the laboratory that will allow us to critically examine the DNA to identify very small changes in the DNA sequence that result in some individuals having an increased risk for a particular disease, such as Parkinson disease.

An important breakthrough that has greatly helped in the development of new methods to analyze DNA was the sequencing of the human genome. One of the unexpected discoveries from the Human Genome Project was that individuals have more variation in their DNA sequence than was originally thought – millions of changes have now been found in the DNA sequence.



Most of these DNA sequence changes are likely to be benign with regard to health, but scientists have quickly learned to use this information to improve the ability to perform scientific research. New methods were developed and gradually improved to the point that we can now test hundreds of thousands of different positions along the DNA sequence in a single laboratory test. It is important to note that even when a researcher is able

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What is PROGENI?

Parkinson's **R**esearch: The **O**rganized **Ge**netics **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, and Cincinnati Children's Hospital.

The PROGENI and PROGENI Cares studies are sponsored by the National Institutes of Health. PROGENI currently involves over families throughout North America who are affected, or possibly affected, with Parkinson's disease. To be eligible to participate in this study, individuals must be affected with, or suspected of having, PD and have a family history of PD. PROGENI Cares now includes nearly 600 individuals with PD and unaffected controls.

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.

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APPROACHES TO DISCOVER GENES

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> **"Researchers have known about the basic structure of DNA for nearly 50 years. However, we have only slowly been able to develop tools and techniques for the laboratory that will allow us to critically examine the DNA to identify very small changes in the DNA sequence that result in some individuals having an increased risk for a particular disease, such as Parkinson disease."**

to test hundreds of thousands of positions along the DNA sequence, there are still millions of positions that are not being tested. We are still just sampling some of an individual's genetic information.

What can we do with all of this new technology?

One of the important things that we want to do is help identify genes that increase the risk for PD. One way to do this is to compare the DNA of individuals with PD with the DNA of individuals who do not have PD. While we cannot compare the entire DNA sequence of the individuals with PD and those without PD, we can compare the DNA at several hundred thousand positions. This is exactly what we are doing in the PROGENI study. We are currently completing a study that compares the DNA at these many different positions in about 500 individuals with PD and 1,000 individuals who do not have PD. We are looking for variations at any one or more of these positions that occur more frequently in individuals with PD than in those without PD. We hope that through this analysis, we can get clues that will help us identify new genes that have made it more likely that some individuals will develop PD and others do not. We hope to have the results of this study by the end of the year.

DEPRESSION IN PARKINSON DISEASE

By Nathan Pankratz, Ph.D., Indiana University

Studies have shown that roughly half of individuals with PD experience depression at some point in their illness. It is increasingly thought of not only as a response to the disease, but also as part of the disease itself.

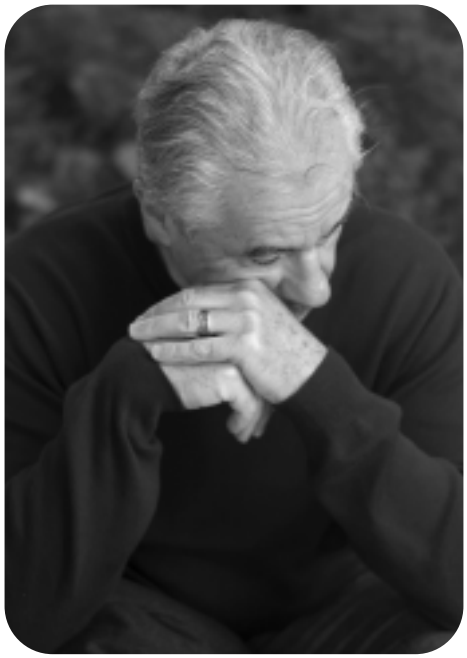
Why might there be a link between depression and PD?

PD affects different parts of the brain. Individuals with PD have a loss of cells in a part of the brain called the substantia nigra. These cells produce dopamine and control movement. In addition, PD also affects cells in the brain that produce chemicals called serotonin and norepinephrine. These brain chemicals influence mood. Therefore, it is not surprising that as PD progresses over time, depression becomes a more common feature.

What have we learned about depression in PROGENI participants?

We recently asked whether PROGENI participants experience more symptoms of depression in the later stages of the disease. As part of the study visit, PROGENI participants were asked to complete a depression questionnaire. We used the information from this questionnaire to classify individuals as either showing signs of depression or not showing signs of depression.

At your study visit, the neurologist completed a scale that allows us to rate each individual's symptoms of PD. This scale is named after its author's, Drs. Hoehn and Yahr. The Hoehn and Yahr scale summarizes the extent of a subject's disability resulting from PD, with scores ranging from 0 (no disability due to PD) to 5 (severe disability due to PD). As is shown in the figure, the percentage of PROGENI participants classified as having depressive symptoms increases as disability increases (i.e. in the later stages of the disease).



When might depression begin in PD patients?

PROGENI data, as well as results from other PD researchers, suggest that the proportion of PD patients having depressive symptoms increases as the disease worsens. However, there have been additional studies that suggest that depression may actually be one of the earliest symptoms of PD, preceding even tremor or slowness of movement. It is important to note that depression does not cause PD. Furthermore, most people with depression will not go on to develop PD. Perhaps most importantly, many individuals with PD will never experience depression or depressive symptoms.

Are there other important risk factors that might tell us who is most likely to develop depression?

Research has shown us that close relatives of individuals with PD not only have an increased risk for PD, but also an increased risk for depression and anxiety. This is further evidence that depression has a biological source and that the source is likely genetic.

Within the PROGENI study, we also tested whether other factors might increase the risk of having depressive symptoms. Some of the factors linked with depression in the general population, like family history of depression, were also associated with signs of depression in the PROGENI study. However, other factors that play a role in the general population, such as being a female or getting older, were not found to increase the risk of depressive symptoms. In the PROGENI study, those subjects requiring greater assistance eating, dressing and performing routine daily tasks had the highest rates of depressive symptoms.

What can you do if you are concerned about depression or depressive symptoms?

One of the challenges of studying depression in PD is that PD symptoms are often very similar to classic signs of depression. For instance, apathy, sleep problems, problems with concentration and slowed movement are frequently seen in PD patients with and without depression. There may also be differences between depression in PD patients and depression in the general population. For instance, there is evidence that depressed PD patients are less likely to have guilt

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THE PARKINSON STUDY GROUP

By Claire E Wegel, MPH, Indiana University

As the PROGENI study reaches its ten-year anniversary, we would like to acknowledge the massive collaborative effort that is required to keep this study running successfully. Over the years, PROGENI study visits have been conducted at as many as 68 Parkinson's Study Group (PSG) sites throughout the United States, Canada, and Puerto Rico. The PSG is a non-profit organization dedicated to PD research and is the primary referral source of participants for the PROGENI study. The PSG currently has a total of 85 active sites in the US, Canada, Puerto Rico and the US Virgin Islands with 350 investigators, coordinators, and other scientists experienced in the treatment and research of PD.

Because PD is a complicated disease with varied forms, symptoms, and rates of progression, studies of PD usually require large numbers of research participants, far more than are typically treated by any single neurologist. It was recognition of this fact that led to the formation of the PSG in 1986. Over the years, the PSG has partnered with the National Institutes of Health and a number of pharmaceutical companies to study new PD treatments. Drugs brought to market with the help of the PSG include pramipexole (Mirapex®), entacpone (Comtan®), rotigotine (Neupro®), and rasagaline (Azilect®).

The PSG not only provides an opportunity to engage large numbers of persons with PD in research but it also provides a framework to ensure that this research meets rigorous scientific standards. Each study is reviewed by a committee of experts in PD treatment and research, and the results of many of these trials have been published in peer-reviewed scientific journals.

> "The PSG aims to advance knowledge about the cause(s), pathogenesis and clinical impact of Parkinson's disease and related disorders and to develop and implement scientific strategies to examine promising therapeutic interventions."
>
> – excerpt from Article I of the PSG constitution

The PROGENI study has a steering committee made up of investigators from the PSG. This group of clinicians and researchers plays an active role in guiding the research directions of the PROGENI study and reviewing PROGENI study manuscripts prior to publication. The PROGENI steering committee is chaired by Dr. Tatiana Foroud and Dr. Ronald Pfeiffer, the Director of the Division of Neurodegenerative Diseases at the University of Tennessee. Other members of the PROGENI steering committee include: Dr. Lawrence Elmer (University of Toledo), Dr. Neal Hermanowicz (University of California, Irvine), Dr. Kelly Lyons (University of Kansas), Dr. Karen Marder (Columbia University), Dr. Frederick Marshall (University of Rochester), Dr. David Oakes (University of Rochester), and Dr. Eric Siemers (Eli Lilly).

For more information about the Parkinson Study Group, its research, participating sites, and publications, please visit http://www.parkinson-study-group.org/

DID YOU KNOW?

- PROGENI enrolled its first family in 1998 and currently has collected information from nearly 850 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 1680 study visits including one in Italy.
- We have collected blood samples from individuals in England, Germany, Israel, India, Ireland, the Philippines, and the Netherlands.
- PROGENI Cares began enrollment in 2004, and 264 people with PD along with 298 healthy controls have completed study visits in the past four years.

EXPANSION OF PROGENI RECRUITMENT

By Tatiana Foroud, Ph.D., Indiana University

For the past decade, PROGENI has only been recruiting families in which two or more living siblings have Parkinson disease (PD). The reason the PROGENI study specifically recruited siblings with PD was that we believed that genetic factors would play a more important role in disease risk when multiple family members had PD. In addition, the technologies available to us over much of the past decade could only study families when there were at least two individuals with PD. Through the involvement of many families having siblings with PD, the PROGENI study researchers have been able to better understand the role of several genes that are important in PD including *LRRK2*, *PRKN* and others.

There are currently 47 PROGENI sites across the United States, Canada, and Puerto Rico.

In the past few years, as described in an accompanying article, *Approaches to Discover Genes that Increase the Risk for PD* there have been major advances in the technologies that can be used to identify genes that increase the risk for diseases such as PD. These technologies have altered the way studies can be designed. The PROGENI study is now making changes that will allow us to involve more families in PD research and still be able to use the most modern technologies available to find genes for PD.

> We are currently working on updating our website, so please check us out on the web to see what's new! http://progeni.iu.edu

We will now be able to enroll individuals diagnosed with PD who also have a parent, sibling or child with PD. In families fitting these criteria, it will now be possible for a single individual with PD to participate. Families having siblings with PD would of course still be eligible to participate in PROGENI, but this new opportunity will allow even more people with PD to take part in this research study. PROGENI will be enrolling individuals, diagnosed with PD, whose parent, child or sibling with PD is either deceased or otherwise unable to complete a study visit him/herself. These individuals with PD would complete a study visit just like other PROGENI study participants.

People who have participated in the PROGENI study are a major source of recruitment for the study. We hope that you will share these new recruitment criteria with any individuals you know who have been diagnosed with PD and who have a positive family history of PD in a parent, sibling or child!

Individuals who would like to participate are encouraged to call 1-888-830-6299 to enroll.

PLEASE WELCOME DR. DRASBY

We would like to take this opportunity to welcome **Dr. Edward Drasby** of Port City Neurology, Inc., Scarborough, ME, to PROGENI. Dr. Drasby and Meg Lannon will now be serving an area previously underserved by PROGENI.

Welcome Dr. Drasby.

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: 305-243-6666 or 800-327-4545

Parkinson's Disease Foundation (PDF)
http://www.pdf.org
Tel: 212-923-4700 or 800-457-6676

Parkinson Disease Information and Resources
http://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] 02 667.13.111 (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

DEPRESSION IN PARKINSON DISEASE

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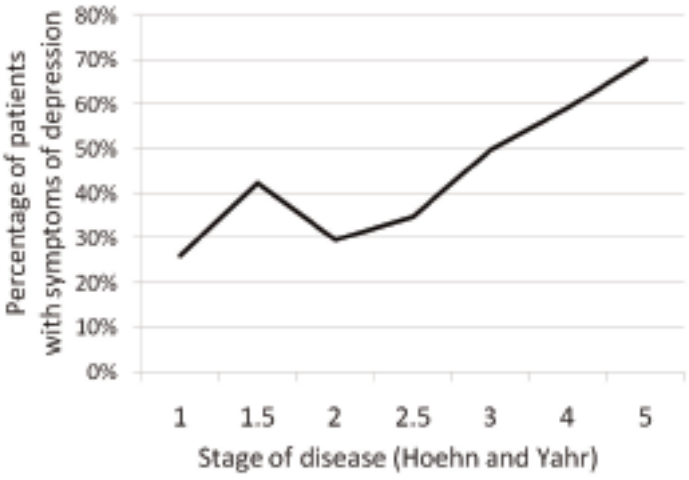
Dr. Pankratz

or suicidal thoughts but are more likely to have anxiety and general apathy. One thing that is true in both groups is that depression is underdiagnosed and undertreated.

If you think that you or someone you care about may be suffering from depression, please speak to your physician and seek out other relevant resources. Because depression is likely due to changes in the neurochemistry of the brain that accompany PD, medication may help. But there are also other effective ways of dealing with the symptoms of depression, including counseling, support groups, stress management and relaxation techniques. Regular exercise can also help improve both the symptoms of depression and the symptoms of PD.



Dr. Pankratz has been with the PROGENI study for five years and performs many of the statistical analyses for PROGENI study publications.

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