

Genetics and Parkinson's Disease: What Have We Learned?

You may have noticed a surge in stories about genetic testing and about specific genes that have been discovered to play a role in diseases. These discoveries, made mostly in the decade since the human genome was successfully sequenced, include 13 gene mutations that are associated with Parkinson's disease (PD).

Whether it is you or your loved one who is living with Parkinson's, you may be wondering how the new genetic discoveries will affect you and what they mean for your own risk or that of your children. In the long run, scientists hope that the knowledge provided by genetics will help us both to diagnose Parkinson's earlier and to slow or stop its progression. They also hope that genetic studies will help us better predict who is at risk for Parkinson's, so that interventions can take place before symptoms develop — but we aren't there yet.

Understanding Categories of Genes

To understand how genes are linked to Parkinson's, think of them in two categories. The first, "causal genes," actually cause the disease. A causal gene alone, without the influence of other genes or environmental factors, guarantees that a person who inherits it will develop PD. This kind of genetic Parkinson's is very rare, accounting for one to two percent of people with PD.

The second category of genes, "associated genes," do not cause Parkinson's on their own, but increase the risk of developing it. A person may have these genes and never develop PD, while people who do not have these genes can still end up being diagnosed with Parkinson's. However, those who have the gene are more likely to develop PD than those without it. In order for associated genes to trigger PD, they probably need to be combined with other genes or environmental factors. For ex-

ample, having genes for fair skin increases your risk of developing skin cancer, but whether you actually develop cancer will depend upon other factors, such as whether or not you spend a lot of time in the sun.

Scientists discovered both kinds of genes by studying families in which many members have developed PD. It may be helpful to look at how some of these families have been affected by genetics.

Causal Genes: Alpha-synuclein

The 'Iowa kindred' or 'Spellman-Muentzer kindred,' as it is known to PD researchers, is a large family in Iowa in which a specific gene for Parkinson's was found. My colleagues and I traced 200 members of the family, including those who developed PD, back to the 1800s and we reviewed medical records dating back to about 1914. Then, taking DNA from blood samples provided by members of the current generation, we tested the entire genome to figure out which genes are associated with PD in this family.

We discovered that the culprit gene in the Iowa kindred was one known as alpha-synuclein, which is located on chromosome 4. Normally, the chromosome carries only a single copy of the alpha-synuclein gene, but members of this family with Parkinson's carried three copies of the gene. This extra dose of alpha-synuclein caused certain family members to develop Parkinson's at a young age.

Even within a family whose members have the same disease-causing gene, individuals may have very different experiences with the disease. In the Iowa kindred, the member of the family who was oldest upon diagnosis was a 51-year-old woman with a form of PD called Lewy body dementia (LBD). Her cousin, however, was just 24 years old when typical Parkinson's symptoms emerged.

Comparing these two people who share the



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same Parkinson's genes, but who experience it differently, can give us clues about the disease. We can hypothesize that the woman who developed LBD at 51 had a genetic or environmental factor that protected her for 20 or 30 years. If we can understand how she was protected from PD, this knowledge could provide valuable insights into how to slow the progress of PD.

Associated Genes: LRRK2

While the gene for alpha-synuclein actually caused Parkinson's in members of the Iowa kindred, another gene called LRRK2 — the gene for the protein Dardarin — is only associated with PD. Mutations in the LRRK2 gene that lead to PD are most common in people of North African, Basque, Portuguese and Ashkenazi Jewish descent, but occur in almost all ethnic groups.

For LRRK2, there is great variability in the mutations that occur in the gene, as well as in their effects. Some people with LRRK2 mutations develop PD in their 30s or 40s, while others develop the disease in their 80s, and others never develop PD at all. In some cases, people with LRRK2 mutations develop dementia, while others develop a form of Parkinson's that shares features with amyotrophic lateral sclerosis (ALS), also known as Lou Gehrig's disease. Understanding why some people develop certain disease features and others are protected, gives scientists clues about how PD starts and progresses.

Using Genetics to Diagnose and Treat Parkinson's

By discovering genes linked to Parkinson's, scientists can develop tests to find out who is at risk of developing it and can begin to diagnose it early, even before symptoms are obvious. Once we find a treatment that can slow down Parkinson's, as opposed to simply easing its symptoms, it will become important to assess genetic risk, and to make a diagnosis as early as possible in order to begin treatment. Genetic research can also provide clues to identifying new therapeutic targets for Parkinson's.

Already, the identification of genes associated with PD has allowed scientists to better understand the disease. For example, the first gene mutation identified to cause Parkinson's was the gene for alpha-synuclein, now known as Park 1. After its discovery, scientists began looking for the alpha-synuclein protein in the brains of people who had died

with PD. They learned that Lewy bodies, the protein clumps that accumulate in dying brain cells, are full of alpha-synuclein. This insight into the basic biological cause of PD has led to ideas for treatments.

The Iowa family studies mentioned above demonstrated that three copies of a normal gene can cause PD. Once this was discovered, the original mutations were re-evaluated, and it was found that both genetic causes increased the amount of synuclein in the cell. Scientists realized that it was the amount of synuclein, not just the type, which led to disease. That understanding, in turn, is leading to strategies which may lessen the amount of synuclein in the cells of people with Parkinson's. It is hoped that someday in the future, this method may help lessen, or hopefully even reverse PD.

Assessing Your Genetic Risk

Am I at risk? Should I get tested? If you or your parent or sibling is living with PD, you have probably asked these questions. You may wonder whether you have passed on risk factors to your children or whether you yourself have inherited any risk. I can relate to this because my own father has Parkinson's. Statistically, my risk is between four and nine percent higher than it would be for a person with no family history of disease. What does that really mean for me? What does it mean for my niece and nephew? The truth is, we don't yet know. Plus, because we lack treatments to slow the development and progression of Parkinson's, genetic testing is not part of routine clinical practice, but is restricted as a research tool. However, ongoing research will refine our knowledge and perhaps provide better answers to these important questions.

Looking Forward

The next time you see genetics and Parkinson's in the news, I hope that you will better understand why this field is so exciting. Discovering Parkinson's genes — both those that cause disease on their own and those that contribute to risk — is helping doctors to better understand PD, to identify the risk of Parkinson's earlier and to treat it more effectively.

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If you have or believe you have Parkinson's disease, then promptly consult a physician and follow your physician's advice. This publication is not a substitute for a physician's diagnosis of Parkinson's disease or for a physician's prescription of drugs, treatment or operations for Parkinson's disease.

