Paths to discovery over time

Predicting Parkinson's disease

When archaeologists begin digging at the suspected site of an ancient city and find only a few pieces of pottery at the surface, they don't walk away dejected saying, "Well, we failed to find the city." They look carefully at the shards of clay and ask themselves, "Is there enough here that we should keep digging?"

Neurologist Demetrius Maraganore, M.D., recognizes the significance a few shards can have. Every day he and his team dig deep and sift through hundreds of thousands of genetic variations and genomic pathways in their quest to unravel the mysteries of Parkinson's disease. Dr. Maraganore is a Mayo Clinic professor of neurology and chair of the Movement Disorders Division. He also is the leader of the worldwide Genetic Epidemiology of Parkinson's Disease Consortium and of Mayo Clinic's Molecular Epidemiology of Parkinson's Disease study.

Demetrius Maraganore, M.D.

"Is there enough here that we should keep digging?"

— Demetrius Maraganore, M.D.

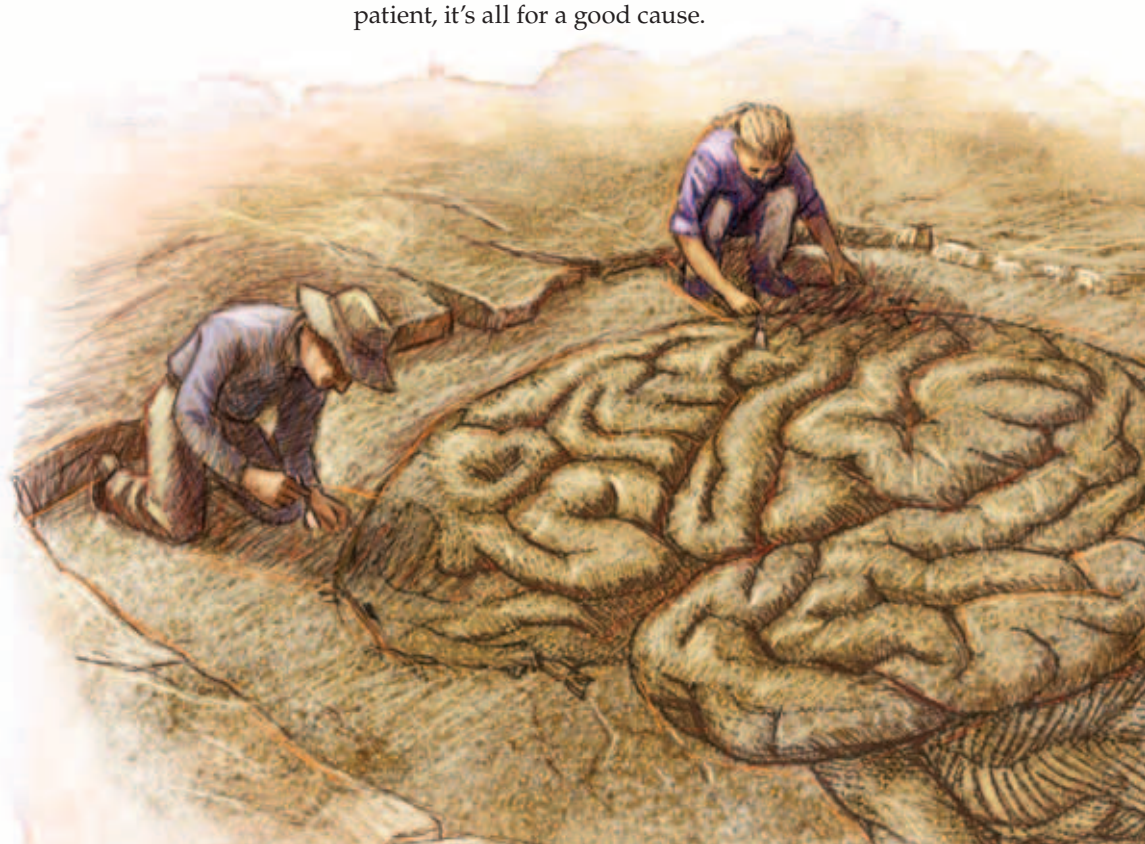

Matthew Farrer, Ph.D.

Excavating from complementary angles

Questions about Parkinson's disease and related disorders are complex and varied. They engage a host of high-level scientists in genetics, pathology and neurology, who each follow different approaches. One group of investigators is finding gene mutations that are unique to certain individuals, families, or special populations including Taiwanese, Ashkenazi Jews, and Tunisians. Matthew Farrer, Ph.D., director of the Division of Neurogenetics, began studying rare instances in which multiple family members had Parkinson's disease. He and his team concluded that Parkinson's disease in those families is caused largely by genetic mutations that pass through scores of related generations over hundreds, if not thousands, of years. Dr. Farrer's team started searching for mutations in genes that caused Parkinson's disease. You name it — they found it: alpha-synuclein, Parkin, SCA2, LRRK2, DCTN1 — a half dozen or more genes in the DNA code that had various "typographical" errors that caused Parkinson's disease in those families.

When Dr. Farrer's colleague, Zbigniew Wszolek, M.D., neurologist and director of Clinical Core of the Morris K. Udall Center of Excellence for Parkinson's Disease Research, began research on the genetics of Parkinson's disease and related conditions, most researchers thought the disease was caused by environmental factors. His experiences challenged that theory. In 1987, he examined a patient diagnosed with Parkinson's disease who reported that many family members suffered from a similar condition. This strong family history stimulated Dr. Wszolek's interest in genetics. He expanded the search through the patient's family tree to more than 300 members and traced the origin of the family to Colonial Virginia. Dr. Wszolek builds a pedigree from a small family and expands it by collecting blood and brain samples and other clinical materials. The goal is to deliver enough material to Dr. Farrer so he can find the gene.

In concert, Dr. Maraganore's team is looking at DNA variations across the entire genome (about 1 billion nucleic acid pairs and 30,000 genes) in thousands of Parkinson's disease cases and control samples from the melting pot of the United States while acquiring insight from the studies of Drs. Farrer and Wszolek that focus on rare families and isolated populations. These complementary approaches among colleagues inspire and stimulate collaboration. It's all about the patient, it's all for a good cause.



Sifting through degrees of mutations

Based on Drs. Farrer's and Wszolek's findings, Dr. Maraganore's team developed a simple hypothesis: If a major typographical error in a gene can cause Parkinson's disease in families, might more subtle errors in those genes render general populations vulnerable, too? The studies uncovered some clues that looked promising, but they didn't stand up to the rigors of replication, or they explained only a small fraction of the risk for Parkinson's disease in the general population. Dr. Maraganore's team decided to approach the problem differently.

Digging with molecular tools on a grander scale

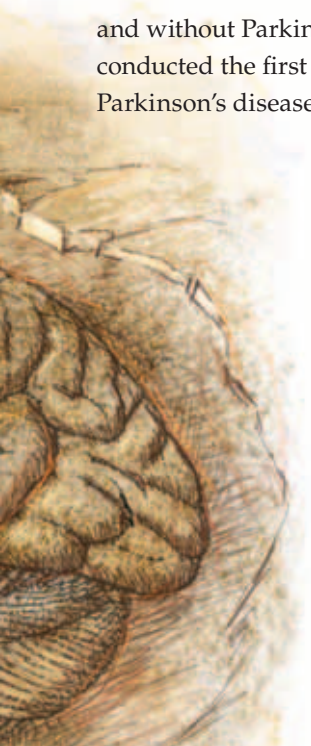
Fortuitously, the DNA microarray technology that became available in the early 2000s allowed Dr. Maraganore's team to measure hundreds of thousands of common genetic variations, called single nucleotide polymorphisms (SNPs), rapidly and affordably. In addition, the federal government and private entities provided billions of dollars to produce a database of human genome variation. This was called the Human Genome Project, which evolved into a broader partnership, the International HapMap Project. The result was a complete "parts list" that helps researchers find genes associated with human disease and their response to drugs. This technology, combined with these bioinformatics, allowed Mayo Clinic investigators to design studies to query hundreds of thousands of genetic variations in people with and without Parkinson's disease. Dr. Maraganore's team conducted the first genome-wide association study of Parkinson's disease — of any brain disease, for that matter.

Zbigniew Wszolek, M.D.

Although the study results were published in 2005, Dr. Maraganore explains, "Our method of analysis of the data was overly simplistic. We looked at about 200,000 genetic variations, and we divided our sample into two subsets. Our study highlighted a dozen 'SNPs,' simple typos in the DNA code that were associated with the risk of developing Parkinson's disease in subset 1, and in subset 2, and in both subsets combined. Only a dozen shards of broken clay! If we looked at the individual effects of any of those variants, they were small. Individually, the SNPs were not useful as methods to predict who would get Parkinson's disease, and they weren't good clues with respect to developing therapies to prevent Parkinson's disease. And, indeed, when other people tried to replicate our findings, they failed." Time to give up? Or to dig deeper?

Untangling wiring cues from "Cry of the Cat"

Research tends to follow a model of one step forward and two steps back. Researchers hope the steps forward are bigger than the two steps back. Fueled by their quest for answers, Dr. Maraganore and his statistician colleague, Tim Lesnick, looked at the 12 or so clues from their genome-wide association study and were most impressed by the findings for a gene called Semaphorin 5A, or SEMA5A. This gene belongs to a family of 128 genes that codes proteins responsible for orchestrating the brain's wiring during fetal development and for repairing that wiring throughout a person's lifetime.



Parkinson's disease is a progressive disorder that affects nerve cells in the part of the brain that controls muscle movement. Symptoms include tremor, slowed movement and rigid muscles. At least 1 million people in the United States are believed to have Parkinson's disease, and 2 percent of the population can expect to develop the disease during their lifetimes.

With each layer of excavation, Mayo Clinic researchers dig deeper into the complex genetic causes of brain diseases to assemble a more complete picture of their origins to help predict, prevent and halt progression.

They learned from the medical literature that a deletion of the SEMA5A gene causes a very rare, fatal genetic disorder called Cri du Chat or "Cry of the Cat" syndrome. This syndrome causes severe abnormality in how the brain is formed. Could it be that subtle variations not only in this SEMA5A gene but in other axon guidance pathway genes predispose people to Parkinson's disease?

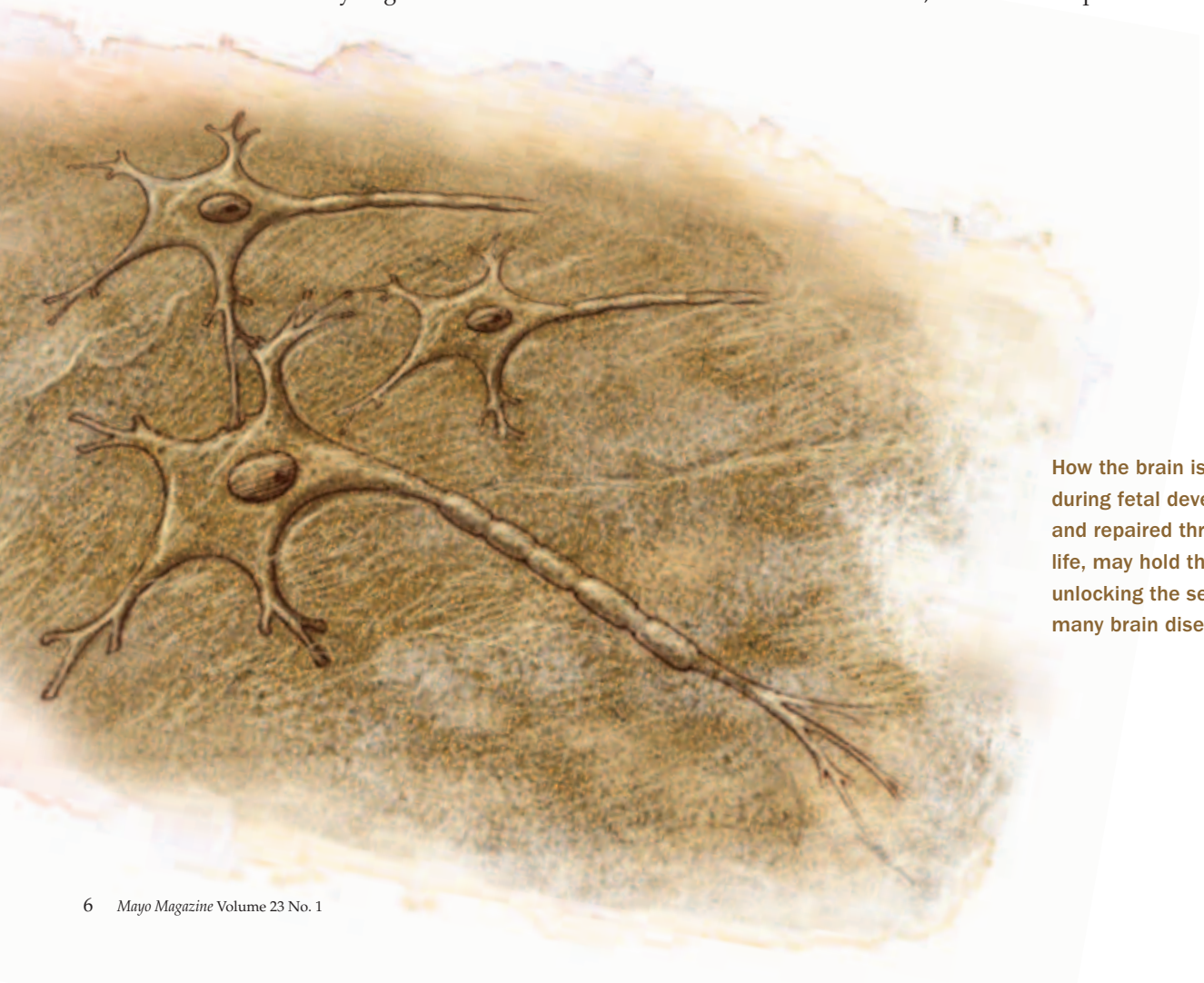
"In fact, our test was so good that we could correctly predict who was at risk, and who wasn't, better than 90 percent of the time."

— Demetrius Maraganore, M.D.

Taking a second look

Dr. Maraganore's team went back to their ill-fated whole-genome study of Parkinson's disease. But, this time they changed perspectives. Instead of looking at just 200,000 variables individually, they looked at the additive effects of variations within 128 genes. Do multiple variations within this axon-guided pathway predict Parkinson's disease?

The results astounded the researchers. "We found that common variations in these genes could identify people who were 90 times more likely to get Parkinson's disease than people who didn't have this profile — kind of like a DNA fingerprint," says Dr. Maraganore. "We found that we could identify, among people with Parkinson's disease, people who as a group had much higher risk and developed the disease as much as 20 years earlier than a group of patients who were considered to be at the lowest risk. And we found that we could predict with 86 percent accuracy the age at which you would actually develop Parkinson's disease. In fact, our test was so good that we could correctly predict who was at risk, and who wasn't, better than 90 percent of the time."



How the brain is wired during fetal development, and repaired throughout life, may hold the keys to unlocking the secrets of many brain diseases.

Ask a bigger question

Although a groundbreaking find, the results pointed to a bigger question. Could the researchers predict Parkinson's disease using axon-guided pathway gene variations in another sample? A year after Mayo's original genome-wide association study of Parkinson's disease was published, the data from a second study was published.

Dr. Maraganore's team took this dataset of several hundred thousand gene variations and asked which variations occur within the 128 axon-guidance pathway genes. The total was about 3,000. Could researchers identify a subset of those 3,000 or so variations that was again predictive of Parkinson's disease?

Yes! Dr. Maraganore's team demonstrated in two different samples of individuals that they could predict multiple Parkinson's disease outcomes by studying common variations in genes in a specific pathway. Other researchers have since used different statistical methods to perform pathway analyses within genome-wide datasets, but the axon guidance pathway is the only pathway that has been associated with Parkinson's disease in multiple datasets and by multiple investigators.

Finding patterns in wiring and repair for other neurological disorders

How the brain is wired and repaired surely isn't important just for Parkinson's disease. What about its importance for other neurological disorders? The Mayo team hypothesized that, just as common variations in axon-guidance pathway genes might predict Parkinson's disease outcomes, they might also predict Lou Gehrig's disease (ALS) outcomes. Lo and behold, by studying common variations in axon-guidance pathway genes in people with and without ALS, the scientists identified a DNA fingerprint, a subset of axon-guidance pathway gene variations that identified people who were 1,000 times more likely to get ALS. Similarly, the tests identified groups of individuals who developed the disease 25 years earlier on average than groups having lower risk.

Once again, the team could predict the age at which people developed ALS with 86 percent accuracy and could, with more than 90 percent accuracy, differentiate people with the disease from control subjects who did not have the disease.

Connecting pathways with diseases

Dr. Maraganore's group is refining its discoveries and extending the same approach to studying seven other diseases: ALS, Alzheimer's disease, stroke, attention deficit/hyperactivity disorder (ADHD), bipolar disorder, major depression and schizophrenia. This team is not looking at axon guidance alone, but at over 200 different pathways that have been annotated in humans, in search of DNA fingerprints that are just as predictive of those seven diseases.

With each layer of excavation, the Mayo team is assembling a more complete picture of the origin of brain diseases. By finding methods to predict these diseases, they create opportunities to prevent their onset or to develop treatments that target disease pathways and halt their progression. ■

Mayo Clinic is featured in the PBS Parkinson's documentary, "My Father, My Brother, and Me," available online at *www.pbs.org/wgbh/pages/frontline/parkinsons.*

How you can help: Contributions to The Campaign for Mayo Clinic help fund this and other areas of genomic research. For more information on how you can contribute, please visit The Campaign for Mayo Clinic Web site at *www.mayoclinic.org/campaign.*