Hunting for the whys of Parkinson's

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A Dartmouth neurologist headed for Amish country to study Parkinson's.

Tremors and rigidity are just a couple of the debilitating symptoms of Parkinson's disease. They're caused by the degeneration of neurons in the brain, but exactly why the brain cells die is largely a mystery. Dartmouth neurologist Stephen Lee, M.D., Ph.D., has been looking for clues to that mystery not only, as one might expect, in his high-tech lab at DMS, but also in an Amish community in Ohio.

Dopamine: Neurons in a part of the brain called the substantia nigra produce a neurotransmitter called dopamine, which communicates with other neurons to control muscles and coordinate movement. Patients with Parkinson's have decreased levels of dopamine, Lee explains, "due to the loss of the neurons that make dopamine." The disease's symptoms can be alleviated by replacing dopamine with drugs. But even with drug treatment, the neurons continue to degenerate and the symptoms to worsen.

"The motivation for a lot of the research is to try to understand the process of neurodegeneration," says Lee. He believes that understanding why dopamine-producing neurons die will eventually lead to better treatments. There are a handful of genes that have been shown to cause Parkinson's to run in some families, but the number of inherited cases is very low. Environmental toxins have also been shown to cause Parkinson's in some instances. However, most cases of the disease are deemed sporadic, meaning there is no identifiable cause.

The data originated amid the haystacks of rural Amish country.

Role: The current thinking in the field is that Parkinson's is caused by a combination of genetic predisposition and environmental exposure; Lee believes that researchers will find "a crucial role for small contributions from many different genes." In an effort to identify some of those genes, Lee and several collaborators at Vanderbilt University developed a project to study the genetics of Parkinson's disease in a large Amish lineage.

There are many advantages to studying genetics in the Amish. Their socially isolated communities are usually descended from a limited number of progenitors, which creates a much simpler genetic pedigree than one finds in modern, mobile populations. In addition, Amish communities keep detailed genealogical records, Amish families are large, new genes are rarely introduced into their population because they seldom marry outside of the Amish community, and they share similar patterns of environmental exposure. All of these factors make them ideal for genetic studies.

Diagnose: To begin his study, which is partly funded by the Michael J. Fox Foundation, Lee travelled to an Amish community in Holmes County, Ohio, to identify individuals with Parkinson's disease. He notes that the Amish were very cooperative and that by conducting thorough examinations, he was able to diagnose Parkinson's in a number of people and distinguish it from other progressive neurological disorders. He then collected DNA from both affected and unaffected family members and analyzed their genealogical records.

Then, says Lee, using a complex method of statistical analysis, "we were able to determine that the cause [of the Parkinson's in the study population] is likely genetic, as opposed to sporadic or environmental."

This was an exciting finding, as it opened up the possibility of identifying a number of genes linked to familial Parkinson's. Identifying genes involved in inherited forms of disease can often lead to insights into the mechanism of the disease in sporadic cases. The same genes and proteins that are altered in inherited cases, in other words, may also be altered in sporadic cases by environmental toxins or other factors. For example, alpha-synuclein, a gene shown to be mutated in some families with inherited Parkinson's disease, was shown to be involved in the normal course of Parkinson's in patients without the inherited mutation.

In his latest paper on the project, published in the journal *Annals of Human Genetics*, Lee and his collaborators identified several DNA regions linked to the risk of getting Parkinson's in this Amish lineage. What exactly is in those regions of DNA? It's unclear at the moment, but the regions span hundreds of genes and are on several different chromosomes, Lee explains.

Genes: "This is only the first step in ultimately identifying the genes that may be responsible for Parkinson's disease in this pedigree," he says. He will continue to analyze the DNA he collected in Ohio, trying to narrow down the affected regions.

Lee likens the effort to looking for a needle in a haystack. When he's working in his high-tech lab, the haystacks are figurative. But the analogy has a literal twist, too, given his data's origins amid the actual haystacks of rural Amish country. KRISTEN GARNER