



Artificial Intelligence Technology Provides New Evidence that Mutations in the Mitochondrial Genome Underlie Parkinson's Disease

Dr. Ben Goertzel

Pope John Paul II suffered from Parkinson's disease, and he was far from alone. Over a million Americans have Parkinson's, and many more suffer worldwide. Yet in spite of years of effort by medical researchers, tracking down the genetic roots of the disorder has proved devilishly difficult. This year, it seems, a combination of human and artificial intelligence may have taken a large step in the right direction.

My colleagues and I at the Maryland bioinformatics firm Biomind, in collaboration with Dr. Davis Parker and his colleagues at the University of Virginia, have applied advanced artificial intelligence technology to analyze data regarding mutations in mitochondrial DNA. And as a result, we have pinpointed a particular region of a particular gene on the mitochondrial genome that appears to be strongly associated with Parkinson's disease.

Parkinson's disease is a progressive disorder of the central nervous system, whose well-known victims – besides the late Pope -- include boxer Muhammad Ali and comedian Richard Pryor. Most common in people over age 45, its symptoms include rigidity, tremors, difficulty with balance and posture, and slowing of movements. Various treatments have been found that lessen the effects of the symptoms, but there is no known cure.

The approach our team has taken for analyzing Parkinson's also has implications for other neurodegenerative diseases. For instance, it seems reasonably likely that applying the same techniques to data obtained from Alzheimer's patients will yield analogous results.

The understanding these results provide is an important step on the path to a cure. It helps scientists understand the mechanisms underlying Parkinson's, which may help with the design of novel drugs. And more speculatively, it may eventually lead to a cure via radical forms of gene therapy. Dr. Rafal Smigrodzi,

a key member of the University of Virginia team underlying the recent discovery, has left UVA to join GENCIA Corporation, a Charlottesville firm developing “mitochondrial gene replacement therapy,” via a novel technique called protofection. Protofection allows the removal of bad fragments of mitochondrial DNA, and their replacement by good ones. If this could be successfully done in living human brains, then potentially Parkinson’s could be cured via gene therapy that simply repairs the flawed regions of mitochondrial DNA located by Biomind’s software.

The story leading up to these recent discoveries is a long and winding one – beginning with a bad batch of heroin, followed by a generous amount of scientific ingenuity, and a synergistic application of human intelligence with advanced artificial intelligence algorithms based on simulation of the evolutionary process.

Parkinson’s is rooted in nerve cells – and is particularly associated with degeneration of nerve cells in the area of the brain governing movement. Thus, if one wants to understand the causes and development of the disease, and ultimately work toward a cure, the obvious place to look is in the genetic material of nerve cells. But the quest for the neurological genetic defects underlying Parkinson’s proved more difficult than anticipated. Scientific discovery comes from multiple sources – human insight, advanced technology, or just plain luck. The identification of the genetic defects underlying Parkinson’s displayed all three.

The lucky break occurred in 1982 – a case where bad luck for drug users was good luck for neuroscientists. Street chemists attempting to create heroin accidentally created a substance called MPTP, which interferes with the function of mitochondria (the cellular components concerned with energy production, often known as the “powerhouses” of cells). Drug users displayed Parkinson’s-like symptoms, including being almost completely unable to move.

What MPTP does is to inhibit the production of a mitochondrial complex called complex I, within nerve cells in the substantia nigra, the brain region responsible for coordinating movement. Complex I contains many enzymes, responsible for reducing a molecule called ubiquinol, which is critical to mitochondrial function. Without adequate production of complex I enzymes, cells can’t properly produce energy. Movement-controlling neurons without enough complex I activity in their mitochondria can’t effectively control movement.

In the words of Dr. Davis Parker, of the University of Virginia – the leader of the UVA component of the research effort that produced the recent discovery, and a visionary of the mitochondria/Parkinson’s connection for close to two decades -- “It was a very important advance in neuroscience done in the name of illicit drugs.” Analysis of the effects of MPTP on drug users Dr. Parker to an intriguing

hunch: if mitochondrial dysfunction yields Parkinson's-like symptoms, then maybe the roots of Parkinson's disease lie in the mitochondrial genome.

The DNA one usually hears about lies in the nucleus of a cell, the cell's center. But mitochondria, the cell's energy-producing engines, also contain a small amount of DNA. The human mitochondrial genome only contains 37 genes (13 of them protein-coding), whereas the nuclear genome contains around 25,000 at last count. But these 37 genes – inherited from the prehistorical time in which mitochondria were independent bacterial organisms -- carry out a lot of valuable functions. If they stop working properly, serious problems can ensue. In 1999, Dr. Parker and Dr. Russell Swerdlow, together with scientists from San Diego firm MitoKor, published work suggesting that defects in the mitochondrial genome may be correlated with Parkinson's disease. Their specific interest was in the 7 mitochondrial genes underlying complex I.

This result has interesting implications for the heredity of Parkinson's. When a baby is conceived, its nuclear DNA is formed by combining nuclear DNA from its mother and its father. Baby's mitochondrial DNA, on the other hand, comes entirely from mom. Thus, these results suggest that Parkinson's may be passed maternally -- but that its defects can skip generations, making the disease appear random.

The work MitoKor did, under Parker and Swerdlow's direction, involved clever manipulations of embryonic human nerve cells. They removed the mitochondrial DNA from the embryonic nerve cells and replaced it with other DNA: sometimes from healthy people and sometimes from Parkinson's patients. What happened was that the nerve cells receiving the mitochondrial DNA from Parkinson's patients started acting like nerve cells on MPTP. Low complex I activity, meaning insufficient energy obtained from mitochondria – and eventually leading to Parkinson's-like sluggishness.

These results were fascinating and suggestive – but where were the actual mutations? All this 1999 work showed was that the problem lay somewhere in the mitochondrial genome. The question was where. Which mutations caused the problem?

To answer this question, Parker and colleagues sequenced mitochondrial DNA drawn from the nerve cells of a number of Parkinson's patients, as well as a number of normal individuals, and looked for patterns. But to their surprise, when in 2003 they set about seriously analyzing this data, they found no simple, consistent pattern. There were no specific genetic mutations common to the Parkinson's patients and not the normal people.

Enter artificial intelligence. Dr. Rafal Smigrodzki, one of Parker's collaborators, was familiar with my artificial intelligence work due to our common participation in

several e-mail lists related to AI advanced technology and futurism. Perhaps, Rafal suggested to me, Biomind technology might be able to find the subtle patterns hidden in the mitochondrial DNA data.

My company, Biomind, had been applying advanced AI techniques to biomedical data since 2001. Our focus was on a different sort of data – “gene expression” data, gathered from devices known as microarrays, which measure how much activity each gene is displaying while a cell is functioning. But my colleagues and I believed we could brew up some custom software capable of solving the Parkinson’s problem.

Appropriately enough, the solution turned out to be a software technique called “genetic algorithms,” which simulates the process of evolution by natural selection – beginning with a population of random solutions to a problem, then gradually “evolving” better solutions via letting the “fittest” solutions combine with each other to form new ones, and making small “mutations” to the fittest solutions. In this case, what the software was “evolving” was potential patterns distinguishing Parkinson’s patients from normal people based on the sequences of amino acids in their mitochondrial DNA. This kind of data analysis is highly exploratory and is never guaranteed to yield a solution – but in this case things worked out happily, and a variety of different data patterns were discovered.

The trick, it turns out, is that while there are no specific mutations corresponding to Parkinson’s disease, there are regions – and combinations of regions -- of the mitochondrial genome that tend to be mutated in Parkinson’s patients. There are many different rules of the form “If there are mutations in this region of this mitochondrial gene and that region of that mitochondrial gene, then the person probably has Parkinson’s disease.” While it took some advanced AI technology to find these patterns, once discovered, the patterns are very easy for non-computer-savvy biologists to understand.

The AI technology was written up in a technical journal article, which will appear later this year in the Journal of Artificial Intelligence in Medicine. But from the point of view of biologists seeking causes and cures for Parkinson’s disease, the technical details don’t matter. Dr. Parker and his colleague Dr. Janice Parks have already published a paper in Biochemical and Biophysical Research Communications, showing that mutations in a certain narrow region of ND5, a mitochondrial gene encoding a complex I subunit, correctly predict whether a person has Parkinson’s disease with 94% accuracy. To discuss these results and others, this June Dr. Parker is convening the First International Brainstorming Conference on Parkinson’s Disease, in Louisville, Kentucky.

These events illustrate the role that artificial intelligence technology has come to play in modern biomedical research. The AI currently used in this context is not “general AI” with autonomy and self-awareness but rather “narrow AI” which is

extremely intelligent at carrying out some particular task – like finding patterns in genomic data. Far from displacing human scientists, AI is serving as IA – intelligence augmentation. With its superior capability to integrate data and detect patterns, AI software helps humans understand the data they've collected, based on the experiments they've designed based on their intuitive insights and their attention to the serendipitous world. The results produced by the AI must then be interpreted by humans – and often-times may be significantly simplified, as in Dr. Parker's selection of a single, simple pattern from the many complex patterns suggested by our Biomind AI algorithms.

A cure for Parkinson's is probably still a fair ways off. But there's no doubt significant progress has been made in understanding the underlying mechanisms. And there's reason to believe similar mechanisms may underlie other neurodegenerative diseases – for example, Alzheimer's. Via deploying a combination of human and computational intelligence, we'll get there – though never soon enough.