Development of parkinson's disease research

The Descendants

In the spring of 1988, neurologist Larry Golbe at the Robert Wood Johnson Medical School in New Jersey conducted a routine examination of a 48-year-old man David. David was diagnosed with PD ten years earlier. A few weeks after the meeting, David died. After the funeral, David’s brother Frank came to see Golbe, as he was concerned that he also might have PD. After giving Frank a full examination, Golbe confirmed that he had the disease, and started a broad family study to search for any other relatives who might have contracted PD. During his examination, Frank told him the family originated in Contursi, a small village in Italy.

Several months after Frank’s visit, Golbe got a visit from a woman with classic symptoms of PD. After Golbe had examined her, he wondered whether there might be something wrong apart from the PD. The patient, Joyce, told him she was of Italian descent, from a small village called Contursi. Golbe immediately made the connection between David and Joyce. He called his senior colleague Roger Duvoisin, and together they embarked on a complex task of medical detection.

A year later, Larry Golbe went to Contursi, Italy to meet with Dr. Salvatore La Sala and his Italian collaborator, the neurologist Giuseppe Di Iorio. They plotted the family tree on a huge chart and found that David and Joyce were seventh cousins. They were two of 574 descendants of a couple who married around 1700. The remarkable finding was that 61 of the recent descendants had developed PD, and that descendants had a 50 percent chance of inheriting the bad gene.

Golbe and his team collected blood samples from members of the kindred to take them to New Jersey for DNA analysis. Such analysis might identify the specific genetic mutation and provide clues as to how it caused PD to develop. In the years ahead Duvoisin’s team failed to capitalize on its discovery because they lacked the specialized skills needed to find the gene.

On August 28, 1995, the National Institute of Neurological Disorders and Stroke (NINDS) held a special workshop about PD. The NINDS director, Zach Hall, had asked Roger Duvoisin to present a progress report on the Contursi kindred. It had now been seven years since they had completed the family pedigree, and people were becoming impatient at the lack of progress. After the meeting, Hall asked Bob Nussbaum, a 46-year-old geneticist from the NIH, if he would be interested in mapping and sequencing the gene. Nussbaum was enthusiastic about the idea and suggested that he worked with his colleague Mihael Polymeropoulos.

The geneticists used a process called linkage analysis to locate the gene. By taking blood samples from large numbers of both affected and healthy members of the Contursi kindred, geneticists can pinpoint the gene to a small region of the genome. Within nine days, Polymeropoulos and Nussbaum found the gene in a small region (band 21) of the long arm (q) of chromosome 4. The genetic “ zip code” is 4q21.

It took another nine months before they located the precise address within the zip code and sequenced the mutated gene. They checked the sequence against GenBank and found a hit. The mutated gene was called SNCA, which coded for a brain protein called alpha-synuclein. A single base change in the gene’s code produced a mutant form of the protein, which caused affected individuals to contract PD.

Maria Grazia Spillantini, an Italian Alzheimer’s researcher working in England, had developed special staining techniques to visualize alpha-synclein in brain tissues. On a hunch, she used the stain to search for alpha-synuclein in brain specimens of deceased PD patients. Even though these patients lacked the Contursi mutation, she found lots of alpha-synuclein. She found it in Lewy bodies. As you recall, Lewy bodies are found inside the brain tissues of PD patients. In 1997 no one knew what Lewy bodies were made of. Spillantini had found the answer: they are made of alpha-synuclein.

Heiko Braak, the legendary neuoanatomist at Goethe University in Frankfurt, was inspired by the discovery that Lewy bodies were made of alpha-synuclein. He embarked on a massive PD project. Using alpha-synuclein staining, Braak looked for Lewy pathology, and he hunted not only in the brain but in the rest of the body. He found that the location of Lewy pathology appeared to change as the disease progressed. Braak argued that this was compelling evidence that PD started perhaps decades before any tremor or rigidity appeared. He suggested that the disease was possibly triggered by an infection in the gut and/or nose and spread throughout the brain in six anatomical stages that mapped into the pattern of symptoms found in epidemiological studies like the Honolulu-Asia Aging Study.

Stage 1: loss of smell and constipation

Stage 2: REM sleep behavior disorder

Stage 3: Classic PD – tremor, rigidity, slowness of movement

Stage 4: Loss of balance

Stages 5 and 6: dementia (when the pathology spreads to the forebrain and the neocortex)

Since the 1997 discovery of the alpha-synuclein mutation, some eighteen potential genetic forms of PD turned up. In 2003, a group of Mayo Clinic and NIH geneticists announced a discovery of another family kindred with an inherited form of PD. The team of geneticists had been hunting for the gene since the mid-1990s. First they looked for gene mutations but found nothing. Eventually they discovered that the Iowa kindred PD wasn’t caused by a point mutation of the gene. They found that affected members of the kindred had extra copies of the normal alpha-synuclein gene on chromosome 4. That means more alpha-synuclein protein is being pumped into the affected individual’s bodies. This discovery showed that you didn’t need a mutation to get PD, too much alpha-synuclein can cause PD.

The discoveries attracted the attention of the Cambridge Professor Chris Dobson. Four decades of research had convinced Dobson that proteins were implicated in a range of diseases – from inherited diseases like cystic fibrosis to neurodegenerative conditions like PD and Alzheimer’s. He speculated that because many diseases appeared to be connected with misbehaving proteins, one day it might be possible to block several of these diseases with a single drug.

Key Takeaways

- In 1997, Larry Golbe discovered the Contursi kindred with an inherited form of PD.
- Mihael Polymeropoulos and Bob Nussbaum pinpointed the mutated gene to a gene called SNCA, which coded for a brain protein called alpha-synuclein.
- Maria Grazia Spillantini discovered that Lewy bodies are made of alpha-synuclein, demonstrating the critical role of alpha-synuclein in PD.
- Heiko Braak classified the pathology of PD into six stages, depending on the pattern of Lewy bodies found in the PD patient.
- In 2003, a group of Mayo Clinic and NIH geneticists discovered another family kindred with an inherited form of PD. The gene is not a mutation of the alpha-synuclein gene. The affected individual has extra copies of the gene in their chromosomes. This discovery showed that you didn’t need a mutation to get PD, too much alpha-synuclein can cause PD.
- The field is now poised to test a series of exciting agents designed to stop the spread of this rogue protein in our bodies and brains.