

# Linking Gaucher and Parkinson's Diseases

December 9 2016, by Ricki Lewis, PhD

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Gaucher (pronounced "go-shay") disease affects one in 450 Jewish people of Ashkenazi (eastern European) descent (one in 10 is a carrier), yet only 1 in 40,000 people in the general population. Of course mutations can happen in anyone, and many people are unaware of having Jewish ancestry. But this rare disease actually impacts a much more common one: being a carrier for Gaucher disease is a risk factor for Parkinson's disease (PD), increasing the likelihood of cognitive impairment.

Two new studies published in the *Annals of Neurology* strengthen the link between the two conditions, and raise familiar issues about the value of genetic testing.

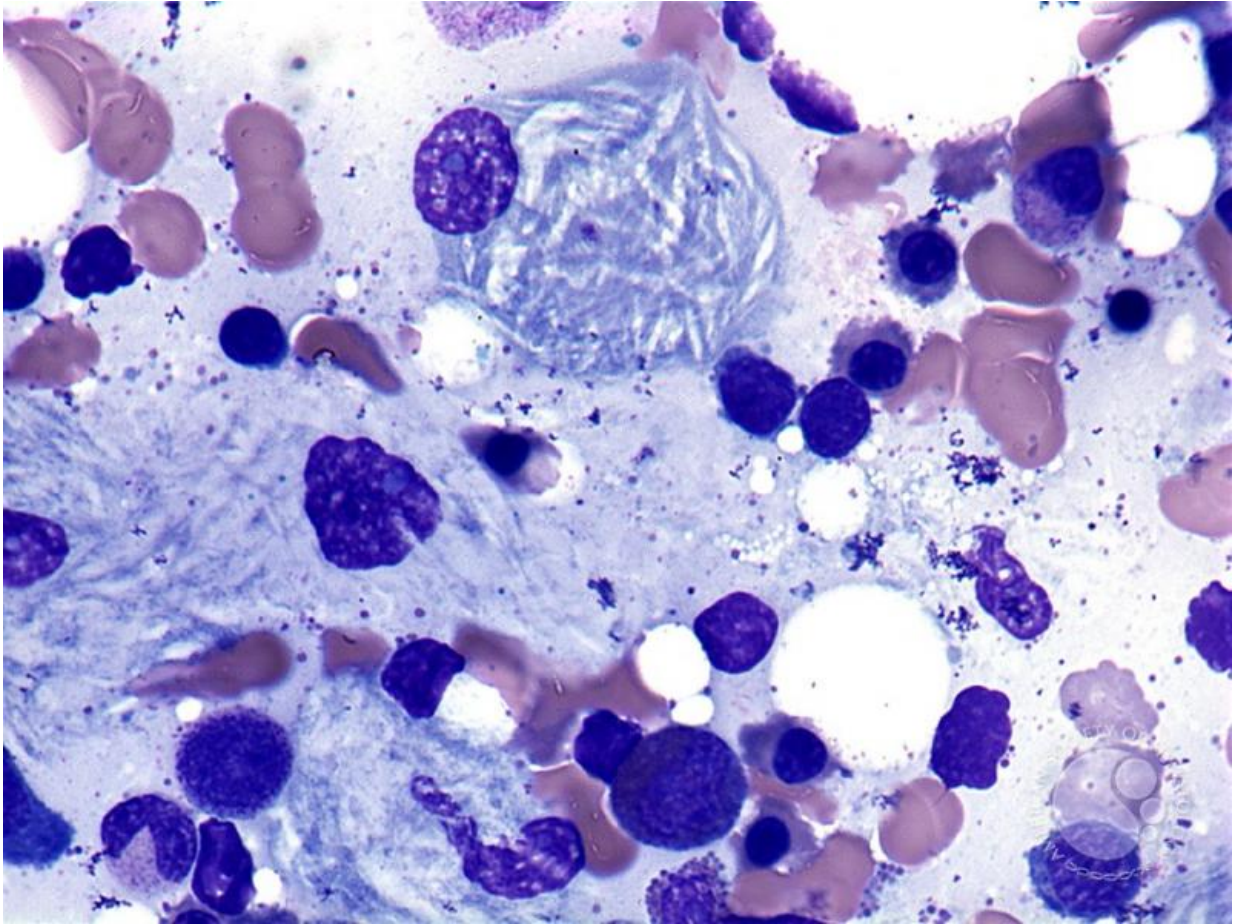
## A storage disease

In Gaucher disease, a deficient enzyme (glucocerebrosidase) causes build-up of glucocerebroside, which enlarges the liver and spleen. Anemia results from too few red blood cells, easy bruising and bleeding from a paucity of platelets, and increased risk of infection from too few white blood cells. Bone and joint pain stem from the blood deficiencies. The disease is very variable in age of onset, symptom severity, and rate of progression.

Gaucher disease is the most common [lysosomal storage disease](#). Lysosomes are debris centers in cells, where enzymes dismantle stuff. When an enzyme is in short supply, the material it normally breaks down builds up. In Gaucher disease, lysosomes swell so greatly that the cells containing them burst. When blobby scavenging macrophages arrive to engulf the mess, they become overwhelmed too, appearing characteristically crinkly.

The enzyme also normally breaks down alpha-synuclein, which forms Lewy body deposits in PD.

Although more than 400 mutations have been identified in GBA, the disease is classified broadly by symptom severity and brain involvement. Type 1, the most common form, had been thought to spare the brain, but more recently has been associated with peripheral neuropathy and parkinsonism.



The large cell in the upper center is a crinkled macrophage. Credit: American Society of Hematology

Despite knowing so much about Gaucher disease, it's still misdiagnosed because the symptoms are so common. That's what happened to 27-year-old Leanna Mullen, who has a video company and works at a high school in TV production.

"I've had a lot of symptoms from the time I was 3 years old, but I wasn't diagnosed until age 15, following a 2 year process with several misdiagnoses. At first doctors thought I had a blood disorder, [Von Willebrand disease](#). They ruled out leukemia. Ultimately a bone marrow

biopsy found that I had Gaucher disease." Her macrophages had the telltale "crinkled paper" appearance.

In retrospect, Leanna's symptoms seem obvious. "My spleen was seven times larger than normal, my liver two to three times larger, and I had a low platelet count," she told me. Leanna's parents and sister are carriers of Gaucher disease, and she has other relatives who have Parkinson's disease. The family isn't Jewish.

## **Treatments, but costly**

Another youngster with a giant spleen who would turn out to have Gaucher disease, and grow up to be the president and CEO of the National Gaucher Foundation, is Brian Berman.

When a bone marrow test diagnosed Brian at age three in 1983, the only treatments corrected the affected body parts: removing the spleen, replacing joints, transfusing blood, or transplanting [bone marrow](#). But a molecular-level treatment was in the works.

The next year Brian became the first person in the clinical trial for enzyme replacement therapy (ERT), developed by a team at Genzyme (now Sanofi Genzyme) led by Roscoe Brady. FDA approved [Cerezyme](#) (imiglucerase) in 1994. Brian and Dr. Brady's intertwined story is told [here](#).



When a bone marrow test diagnosed Brian at age three in 1983, the only treatments corrected the affected body parts.

The brave little boy was the only child among the 8 participants in the trial. Today, like others with Gaucher disease, he leads a near-normal

life – just experiencing some joint pain and slightly weakened immunity – thanks to ERT.

Leanna Mullen has received Cerezyme in a four-hour infusion every other week since 2005. "My spleen is back to normal size, liver same thing and the bone density hasn't gotten worse," she told me. But it costs [\\$300,000 a year](#).

Another type of drug, given orally, reduces glucocerebroside rather than replacing the enzyme, and is a "substrate reduction therapy." It has an even higher price tag. Ads are especially [jarring](#): for a 90-day supply of Zavesca (miglustat) "pay the discount price of \$27,684.60" at Wal-Mart, for example. Another substrate reducer is Cerdelga (eliglustat).

## The Parkinson's connection

In the 1990s physicians began to notice patients with both Gaucher and Parkinson's. A [1996](#) report described 6 people with Gaucher disease as well as early onset, severe PD with cognitive decline. Then a 2003 investigation associated being a [carrier for Gaucher](#) with increased risk of PD. A [2007 study](#) linked glucocerebrosidase deficiency and synuclein accumulation.

The two reports and commentary in the November *Annals of Neurology* strengthen the association between the two diseases.

One study, from the Ann Romney Center for Neurological Diseases at Brigham and Women's Hospitals and the International Genetics of Parkinson Disease Progression Consortium, with funding from the Michael J. Fox Foundation (MJFF), sequenced all coding regions of the gene and ranked mutations by "neuropathic" effect on cognition and memory. Of 2,304 Parkinson's patients from the US, Canada and Europe, 10% were either carriers of Gaucher disease or actually had it.



Dr. Roscoe Brady led research in developing enzyme replacement therapy for Gaucher disease.

The risk of developing global cognitive impairment within ten years of PD diagnosis was 50 percent for patients carrying a neuropathic mutation, but 20 percent for Parkinson's patients without such a mutation. By age 70, more than 70 percent of PD patients with neuropathic mutations develop dementia.

The second study, from researchers at the Parkinson Institute in Milan, sequenced part of the gene and classified mutations by effect on enzyme level. Their findings were similar to the US results: Carriers of neuropathic mutations who have PD are at greater risk of dementia and death. Overall, such a mutation triples risk of global cognitive

impairment.

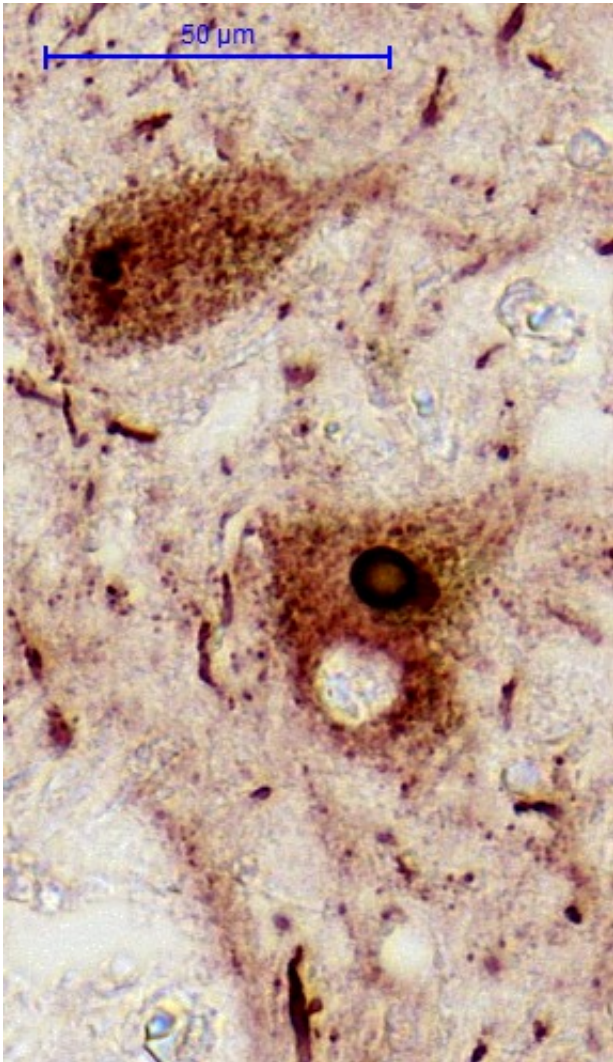
But interpretation requires perspective: Only 10% of PD patients have GBA mutations, and only 10-20% of them experience cognitive decline – that's just 1-2% of all the patients studied. Perhaps variants in other genes protect patients who have neuropathic GBA mutations but normal cognition.

## **The bigger picture: allelic diseases**

"Allelic diseases" are different clinical conditions resulting from mutations in the same gene. Often one is rare, the other not, such as the duo of Gaucher and Parkinson's.

As more human genomes are sequenced, more gene variants and their functions identified, and "connectomes" of gene expression constructed, the list of allelic diseases will grow.

Designating allelic disease pairs reflects semantics and the timing of discoveries as well as science. Consider [cystic fibrosis](#) (CF) and sickle cell disease (SCD). Different CFTR genotypes (mutation combinations) cause very distinct phenotypes – from the classic "salty sweat" and clogged lungs, to chronic sinusitis and bronchitis, or just male infertility – yet they're all CF. But mutations at different sites in the [beta globin gene](#) cause two distinct diseases, SCD or beta thalassemia, although both are anemias.



Lewy bodies in PD

Allelic diseases may represent an intersection of a [rare disease](#) with a more common one. Typically, a rare inherited disease is caused by mutation in a single gene, revealing the mechanism of the pathology. An associated common condition, such as PD, tends to reflect several risk genes as well as environmental influences. In terms of numbers, then, a David can inform on a Goliath: Gaucher affects 6,000 people in the US compared to Parkinson's million.

The link between the two diseases may have practical repercussions. Should patients with Parkinson's disease take a Gaucher carrier test?

A predictive test for a condition with no way to prevent, delay, or treat symptoms is a familiar dilemma in medical genetics. The situation for PD isn't as clear cut as it is for [Huntington Disease](#), in which inheriting a mutation is a genetic near-guarantee of developing the condition. Murkier is detecting the [ApoE4](#) gene variant that indicates increased risk of Alzheimer's disease. And whatever the disease, preferring not to know is as valid an option as wanting to know everything possible.

On the research front, however, the link between the two diseases is a great opportunity to stratify Parkinson's patients by GBA genotype, to test drug candidates to prevent, delay, or otherwise counter the [cognitive decline](#). The MJFF has formed an international consortium of "GBA-PD" cases and controls to do just that.

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