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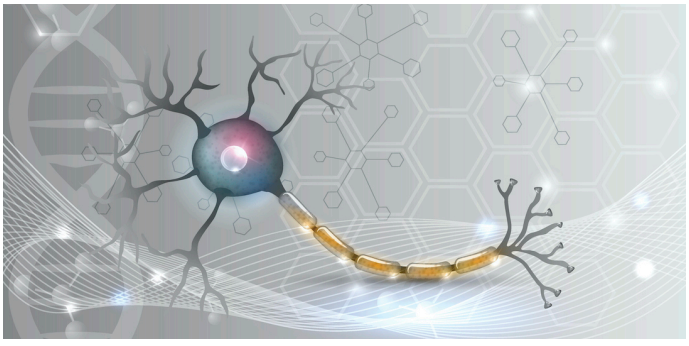
Innovative Genetic Research May Lead to Treatment for Inherited Form of Peripheral Neuropathy

Reversing high sugar levels is thought to be key to preventing nerve damage in diabetes. The very same sugar metabolism pathway has now been linked directly to an inherited form of peripheral neuropathy. This will likely change the view on molecular underpinnings of diabetes-induced nerve damage.

Finding a key genetic mutation, devising a pre-clinical model analogous to what happens in humans, and demonstrating that available medications could work in this population are among the novel discoveries reported in the prestigious journal *Nature Genetics* on May 4. The advances emerged through a unique interdisciplinary collaboration between two teams of University of Miami Miller School of Medicine researchers.



UM researchers are looking at nerve cell genetic mutations to learn more about peripheral

neuropathy.

Uncovering the genetic changes driving Charcot-Marie-Tooth (CMT) disease, a specific group of inherited peripheral neuropathies, is a research focus of Stephan Züchner, M.D., Ph.D., professor of human genetics and neurology and chair of the Dr. John T. Macdonald Foundation Department of Human Genetics, and his team at the Miller School.

Interestingly, the relevant sorbitol dehydrogenase (SORD) mutations were hidden from the gene analysis software most researchers use. The UM researchers used a different strategy, and found the relevant variations hidden behind a "pseudogene" called SORDP2. Pseudogenes are portions of the chromosome that lack function but mirror the DNA sequence of their active counterparts.

Finding this elusive pathogenic SORD allele, inherited in a recessive trait, was one of the surprising novel findings of the study. Next, Dr. Züchner and team identified 45 individuals from 38 families who featured this specific biallelic mutation. All 45 people were diagnosed with CMT, including 69% of cases considered sporadic (people with no known family history of neuropathy). Some diagnoses were based on presence of a slowly progressive neuropathy, often starting with foot deformities.

Dr. Züchner and team had access to large amounts of genetic data from patients with rare diseases collected by the Inherited Neuropathy Consortium, the Asian and Oceanic Neuropathy Consortium, and others. Key to this discovery were Adriana Rebelo, Ph.D., associate scientist at the Hussman Institute for Human Genomics, and Andrea Cortese, M.D., a

visiting scholar from University College of London.

However, what Dr. Züchner and team did not have was a suitable pre-clinical model to take the research further. “An animal model is great because you can study the nervous system directly,” he said.

That’s when he encountered R. Grace Zhai, Ph.D., senior associate dean for basic science research and associate professor in the Department of Molecular and Cellular Pharmacology at the Miller School. Dr. Zhai runs a basic science laboratory across the street from Dr. Züchner’s research team.

“I ran into Grace over lunch and told her about the discovery. And she said she could put the gene mutation into her fly model,” Dr. Züchner said.

“What we found in the paper is this really remarkable phenotype using the Drosophila compound eye. Each eye has about 800 small eyes,” Dr. Zhai said. “If a subtle change is repeated or amplified 800 times, I bet you, you will pick it up.”

The Charcot-Marie-Tooth nerve damage tends to get progressively worse over time in people. The same loss of nerve synapses over time was observed in the fruit fly model, Dr. Zhai reported.

The fruit fly has another “great advantage,” she said. Dr. Zhai and colleagues were able to genetically manipulate the fly to make the gene responsible for metabolizing sorbitol. As a result, sorbitol levels shot up and damaged the neurons.

Importantly, the elevated sorbitol levels caused precisely the same kind of damage observed in people. “Via the power of inherited diseases analysis, this proves for the first time directly that higher sorbitol levels damage your peripheral nerves,” Dr. Züchner said. “Curiously there are some profound differences to the typical nerve damage observed in diabetic neuropathy.”

Furthermore, using existing medications, aldose reductase inhibitors that were developed to reduce elevated sorbitol in people with diabetes, sorbitol levels dropped to near normal in the fruit fly. This was another major discovery in the paper – that this class of drugs already approved for use in India, China and Japan could prove effective to treat peripheral neuropathy.

“We were very lucky – there is already a drug available that works exactly where we want to target. So we could quickly test this drug to show that it is effective,” Dr. Zhai said.

“We’re very optimistic about the therapy going forward,” Dr. Züchner said. “In the fly, the drug basically cured the disease.”

The fruit flies with neuronal damage also behaved differently, but when treated, showed an “amazing reversal” of their altered movements, Dr. Zhai said. “This is truly remarkable. In my career I work on neurodegenerative diseases, and I’ve never seen such complete suppression of the phenotype. We are very excited about this.”

Following the genetic discovery in people and modeling CMT in fruit flies, the next step was to go back to humans, in

cultured cells.

Dr. Züchner and team used skin cell fibroblasts from affected patients. Just as in the fruit fly model, when relevant genes were inactivated, they saw accumulation of the sorbitol and reversal with addition of the medication.

“It’s a complete cycle of discovery and then informed therapy,” Dr. Zhai said.

Furthermore, because sorbitol levels so closely aligned with damage to the nerves, the amount of sorbitol circulating in a person’s blood was shown by the team to be increased over 100-fold in patients. This could serve as a valuable biomarker.

“This story is really unique. Because we can measure the sorbitol, we will be able to determine effectiveness of treatments and even can determine pathogenicity of DNA variants,” Dr. Züchner said. Measuring sorbitol levels in a blood sample could flag people at risk and could also help physicians monitor response to treatment over time.

The collaborative environment at the Miller School was essential to this series of novel discoveries, Dr. Zhai said. “This wouldn’t have happened without our collaboration. I wouldn’t have known about it.”

Other faculty from the Miller School include Mario Saporta, M.D., assistant professor of neurology, who built and runs the premier CMT clinic in Florida. He also is an expert in stem cell research of motoneurons and is already working on a so-called neurosphere model of SORD. Further, the environment for rare disease research is significantly supported by the Miller

School site of the Undiagnosed Disease Network led by Mustafa Tekin, M.D., and Dr. Züchner.

Determining the mechanism behind how sorbitol damages neurons and how the gene mutation orchestrates such actions could be evaluated in future research.

The core study team included Michael Shy, M.D., from the University of Iowa, and David Hermann, M.B.B.Ch., from the University of Rochester. Dr. Züchner added, “Without the support of the Inherited Neuropathy Consortium, this work would not have been possible.”