Researchers discover gene crucial for nerve cell insulation

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Researchers funded by the National Institutes of Health have discovered how a defect in a single master gene disrupts the process by which several genes interact to create myelin, a fatty coating that covers nerve cells and increases the speed and reliability of their electrical signals.

The discovery has implications for understanding disorders of myelin production. These disorders can affect the peripheral nervous system—the nerves outside the brain and spine. These disorders are known collectively as peripheral neuropathies. Peripheral neuropathies can result in numbness, weakness, pain, and impaired movement. They include one of the most common genetically inherited disorders, Charcot-Marie-Tooth disease, which causes progressive muscle weakening.

The myelin sheath that surrounds a nerve cell is analogous to the insulating material that coats an electrical cord or wire, keeping nerve impulses from dissipating, allowing them to travel farther and faster along the length of the nerve cell.

The researchers discovered how a defect in just one copy of the gene, known as early growth response gene 2 (EGR2) affects the normal copy of the gene as well as the functioning of other genes, resulting in peripheral neuropathy.

"The researchers have deciphered a key sequence essential to the assembly of myelin," said Duane Alexander, M.D., Director of the NICHD, the NIH institute that funded the study. "Their discovery will provide important insight into the origins of disorders affecting myelin production."

The study appears in the online version of *Molecular and Cellular Biology*.

John Svaren, Ph.D., an associate professor in the Department of Comparative Bioscience at the University of Wisconsin–Madison's School of Veterinary Medicine, worked with colleagues Scott E. LeBlanc, and Rebecca M. Ward, to conduct the study. Dr. Svaren is an affiliate of NICHD-funded mental retardation and developmental disabilities research center at the Waisman Center at the University of Wisconsin.

Until this discovery, researchers did not fully understand the complex genetic process that enables Schwann cells, found in the peripheral nervous system, to coat nerves with myelin.

During this study, the scientists found that EGR2 produces a protein that activates several other genes necessary for myelin production. Some of these genes contain the information needed to make peripheral myelin protein 22 (PMP-22) and myelin protein zero (MPZ). MPZ is the most abundant protein in myelin in the peripheral nervous system.

The overproduction or underproduction of the proteins PMP22 and MPZ account for the majority of inherited peripheral neuropathies, Dr. Svaren said.

Ultimately, the sequence of activating genes "switches on" the Schwann cell, which wraps the nerve axon, the arm-like projection that conveys nerve impulses, in a myelin sheath.

The scientists' research also resolved a long-standing mystery surrounding why a single mutant copy of the EGR2 gene disrupts the functioning of the normal EGR2 gene, leading to a disorder of the nervous system.

In many genetic conditions, the unaffected copy of an affected gene continues to produce its protein. However, the researchers found that the mutant EGR2 copy interferes with the interaction between the normal EGR2 gene and another myelin gene, SOX10, as the two try to work together to produce the myelin protein MPZ.

By understanding the process which creates myelin, researchers may now be able to investigate new therapies for disorders affecting myelin.

"Our research has uncovered a whole new mechanism for regulating myelin genes," said Dr. Svaren. "Our hope is to exploit this knowledge so that we can adjust the levels of myelin genes such as PMP22 and MPZ, and thereby create an effective treatment for myelin diseases."

Understanding the process by which nerve cells are myelinated also could be applied to other disorders as well, Dr. Svaren said. Diabetic neuropathy, which results in a loss of feeling in the extremities, also is thought to involve myelin production.

Dr. Svaren added that it is possible that the current study's findings about myelin production in the peripheral nervous system could lead to greater understanding of how myelination takes place in the central nervous system (the brain and spinal cord). Myelination in the central nervous system is not well understood. Multiple sclerosis, a degenerative muscular disorder that can be fatal, results from the destruction of myelin in the central nervous system.

Source: National Institute of Child Health and Human Development