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'Rare' brain disorder may be more common than thought: study

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A global team of neuroscientists, led by researchers at Mayo Clinic in Florida, have found the gene responsible for a brain disorder that may be much more common than once believed. In the Dec. 25 online issue of *Nature Genetics*, the researchers say they identified 14 different mutations in the gene CSF1R that lead to development of hereditary diffuse leukoencephalopathy with spheroids (HDLS). This is a devastating disorder of the brain's white matter that leads to death between ages 40 and 60. People who inherit the abnormal gene always develop HDLS. Until now, a definite diagnosis of HDLS required examination of brain tissue at biopsy or autopsy.

The finding is important because the researchers suspect that HDLS is more common than once thought and a genetic diagnosis will now be possible without need for a brain biopsy or autopsy. According to the study's senior investigator, neurologist Zbigniew K. Wszolek, M.D., a significant number of people who tested positive for the abnormal gene in this study had been diagnosed with a wide range of other conditions. These individuals were related to a patient known to have HDLS, and so their genes were also examined.

"Because the symptoms of HDLS vary so widely — everything from behavior and personality changes to seizures and movement problems — these patients were misdiagnosed as having either schizophrenia, epilepsy, frontotemporal dementia, Parkinson's disease, multiple sclerosis, stroke, or other disorders," says Dr. Wszolek. "Many of these patients were therefore treated with drugs that offered only toxic side

effects.

“Given this finding, we may soon have a blood test that can help doctors diagnose HDLS, and I predict we will find it is much more common than anyone could have imagined,” he says.

Dr. Wszolek is internationally known for his long-term efforts to bring together researchers from around the world to help find cases of inherited brain disorders and discover their genetic roots.

Dr. Wszolek’s interest in HDLS began when a severely disabled young woman came to see him in 2003 and mentioned that other members of her family were affected. The diagnosis of HDLS was made by his Mayo Clinic colleague, Dennis W. Dickson, M.D., who reviewed the autopsy findings of the patient’s uncle, who had previously been misdiagnosed as multiple sclerosis, and subsequently, Dr. Wszolek’s patient and her father. All members of the family had HDLS.

Dr. Dickson had identified other cases of HDLS from Florida, New York, Oregon and Kansas in the Mayo Clinic Florida brain bank and knew of a large kindred in Virginia with similar pathology, based upon a presentation at the annual meeting of the American Association of Neuropathologists. With concerted efforts, Dr. Wszolek and collaborators at University of Virginia were able to obtain DNA samples from the Virginia kindred. Dr. Wszolek also sought other cases, particularly those that had been reported in the neuropathology literature, and he was able to obtain samples from Norway, the United Kingdom, Germany and Canada, and other sites in the U.S. He and his team of investigators and collaborators have since published studies describing the clinical, pathologic and imaging characteristics of the disorder, and they have held five international meetings on HDLS.

In this study, which included 38 researchers from 12 institutions in five

countries, the study's first author, Rosa Rademakers, Ph.D., led the effort to find the gene responsible for HDLS. Her laboratory studied DNA samples from 14 families in which at least one member was diagnosed with HDLS and compared these with samples from more than 2,000 disease-free participants. The gene was ultimately found using a combination of traditional genetic linkage studies and recently developed state-of-the art sequencing methods. Most family members studied — who were found to have HDLS gene mutations — were not diagnosed with the disease, but with something else, thus emphasizing the notion that HDLS is an underdiagnosed disorder.

The CSF1R protein is an important receptor in the brain that is primarily present in microglia, the immune cells of the brain. "We identified a different CSF1R mutation in every HDLS family that we studied," says Dr. Rademakers. "All mutations are located in the kinase domain of CSF1R, which is critical for its activity, suggesting that these mutations may lead to deficient microglia activity. How this leads to white matter pathology in HDLS patients is not yet understood, but we now have an important lead to study."

"With no other disease have we found so many affected families so quickly," says Dr. Wszolek. "That tells me this disease is not rare, but quite common." He adds, "It is fantastic that you can start an investigation with a single case and end up, with the help of many hands, in what we believe to be a world-class gene discovery."

Provided by Mayo Clinic