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Researchers suspect a novel gene is causing restless legs syndrome in a large family

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In 2005, a woman who had trouble sleeping asked Siong-Chi Lin, M.D., for help. Dr. Lin, a sleep disorders specialist at the Mayo Clinic campus in Florida, diagnosed restless legs syndrome. This common neurologic disorder interrupts sleep because of unpleasant sensations in the legs at rest, especially in the evening, that are temporarily relieved by movement.

Restless legs syndrome affects between 5 and 11 percent of the population in North America and Europe, says Dr. Lin. The cause may be a number of clinical factors, such as iron deficiency, but it has a strong genetic component as well. "In most people, it is likely due to a number of different causes, but genes are very likely the most important factor in affected families," he says.

Medications, especially agents that increase transmission of dopamine in brain neurons, are effective in many people and worked for his new patient, says Dr. Lin. "The syndrome may appear as a nuisance for most people, however it can also seriously affect some people's quality of life," he says.

Dr. Lin's patient told him that many of her relatives also have the same trouble sleeping — difficulties she could trace back through her ancestry.

With the patient's approval, that information was relayed to "gene hunters" in Mayo Clinic's neurosciences department. These investigators

have established an international reputation for their ability to find the genetic roots of rare, as well as common, neurological disorders. Dr. Lin accompanied investigators to Indiana, the hub of the extended family, which is believed to be of English descent, to interview dozens of individuals spanning multiple generations. They found that 30 relatives were affected by restless legs syndrome, and discovered that almost three times as many females had the condition compared to males.

Now, the researchers are reporting in the February issue of *Mayo Clinic Proceedings* that the restless legs syndrome found in this family is likely due to a gene mutation that has never been linked to the disorder.

To date, five loci, or areas on the genome, have been linked to restless legs syndrome in other families around the world, but this family does not have any of those mutations.

"That means this family likely has a novel gene that is causing the disease," says the study's lead investigator, Carles Vilariño-Güell, Ph.D., a neuroscientist at Mayo Clinic's campus in Jacksonville. The researchers have not yet pinpointed the culprit gene, but say they are getting close.

This study is important, Dr. Vilariño-Güell says, because this family is one of the largest with restless legs syndrome ever studied, and the disorder spans multiple generations. Therefore, the gene linked to the syndrome is widespread among the affected relatives, increasing the chances that the researchers will soon zero in on the gene responsible.

"With so many people in this family affected by the syndrome, we have a lot of power to find the gene mutation causing disease," he says.

Once a gene is discovered, researchers can investigate its normal function and the mutation's effect, and then can "try to overcome that

problem with drug therapy," he says. They can also trace the molecular route from the gene mutation to the disorder, and see if the other loci linked to the syndrome lie along this pathway. So far, no one has found a definitive link between restless legs syndrome and a specific gene mutation, but large families hold the clues for these discoveries, says Dr. Vilariño-Güell.

Source: Mayo Clinic