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GENE VARIANT FOR RESTLESS LEGS SYNDROME DISCOVERED: *Variant provides insight into likelihood of developing RLS*

ROCHESTER, MN – July 18, 2007 – The Restless Legs Syndrome Foundation is proud to announce the discovery of the first gene variant that contributes substantially to risk for restless legs syndrome (RLS). This study was supported in part by a grant from the RLS Foundation and was conducted by physician researcher and RLS Foundation Board member, David Rye, M.D., Ph.D. and his collaborators at deCODE Genetics in Reykjavik, Iceland.

The results of this study, headed jointly by deCODE Genetics and Dr. Rye, of Emory University in Atlanta, Georgia appear in the online edition of the prestigious *New England Journal of Medicine* and will also appear in print in the August 16th edition of the Journal. Two editorials accompanying the article, as well as one appearing simultaneously in *Nature Genetics*, speak to the influential nature of this and corroborating findings in Germans and French-Canadians. These findings and the technology behind them are ground-breaking, not only to the RLS community, but to the entire field of medicine.

The results of Dr. Rye's and deCODE's study revealed the discovery of a gene variant that appears to be the primary contributor to RLS. This discovery still allows for the possibility that additional genes might influence RLS in smaller ways. The variant is extremely common—nearly 65% of the population of Iceland and the southeastern United States carry at least one copy of the variant. This finding explains why RLS is so common. In addition, the variant appears to be much less common in Asians (~35%), helping to explain the lower prevalence of RLS in Asia.

To find this genetic variant, Dr. Rye and colleagues evaluated subjects with RLS who also had periodic limb movements in sleep (PLMS), unconscious movements of the legs during sleep that are measured objectively. PLMS are present in about 90% of people with RLS and are considered a typical expression of RLS. Rye and deCODE colleagues studied (1) RLS with PLMS subjects and (2) control subjects. They not only discovered this genetic variant but were able to replicate the findings in two additional subject groups: one in Iceland and one in the U.S.

One way to assess the impact of the gene variant upon disease is through calculation of the “population attributable risk.” This is the proportion of RLS cases that would disappear if the identified variant were removed or replaced by what is present in the control population. According to the findings of this study, a conservative estimate is that 50% of all RLS with PLMS would disappear if this gene variant were eliminated.

This discovery also provides new information about a person’s risk for developing RLS. Dr. Rye and colleagues discovered that the number of gene variant copies a person carries from birth influences his or her risk of developing RLS. One copy of the variant results in a nearly two-fold risk, and two copies of the gene variant results in as high as a four-fold risk for developing RLS.

It is important to emphasize that having one or two copies of this gene variant does not mandate that a person will develop symptoms of RLS. According to Dr. Rye, “There remain medical, environmental and additional genetic factors that one is prone to in life that translate this risk into RLS symptoms. Examples include iron deficiency, kidney disease, diabetes, neuropathy, etc.—all factors that clinicians have long suspected to be associated with RLS.”

The study clearly demonstrates that having two copies of the gene variant influences the severity of the condition. Dr. Rye’s study found that people carrying two copies of the variant have more severe symptoms as reflected in their number of periodic limb movements of sleep (PLMS).

Lewis M. Phelps, Chair of the RLS Foundation Board of Directors, commented, “This ground-breaking discovery by Dr. Rye and his colleagues significantly advances our understanding of

the cause of RLS and paves the way for both improved diagnostic methods and better treatment for those living with RLS.”

“Fifteen years ago, restless legs syndrome was a little-known and often misunderstood condition,” Phelps continues. “People with RLS suffered severe disruption in their lives including chronic lack of sleep, debilitating fatigue, and inability to participate in activities that required prolonged sitting without movement, such as movies and airplane flights. Today, RLS is better understood and more frequently diagnosed accurately; improved treatments are also available. However, much remains to be done before we conquer RLS,” Phelps said.

This discovery is more than just a step forward. It represents a gigantic leap in our understanding of this complex disorder. While further research is needed to determine exactly how this genetic variant translates into RLS symptoms, understanding this mechanism will lead to better treatments, prevention, or a cure. Dr. Rye and colleagues have found that the gene variant is more common in Icelanders with low iron—which has already been associated with RLS. Ongoing studies are examining the relationship of this variant to iron metabolism.

The discovery also raises the question of whether genetic testing could now be used to screen for RLS. Since having one or two copies of the gene does not ensure the development of RLS, genetic testing to screen for RLS is not likely to see widespread use. However, Dr. Rye notes that genetic testing could be used to help assess RLS severity and develop treatment strategies for those who have already developed RLS. Testing could be particularly insightful in situations where the risk of RLS is already high such as kidney failure and in children where diagnostic tools are less well developed.

This work was funded by the RLS Foundation and other private sources and will require increased investment to expand upon these seminal findings. The RLS Foundation has funded nearly 30 deserving grants, like Dr. Rye’s, which offer the opportunity to participate in advancing our understanding of RLS. “The Foundation is extremely excited to learn of the results of this study,” said Georgianna Bell, Executive Director of the RLS Foundation. “It is further encouragement to the

Foundation and its members that the monies we are devoting to research are integral to the future of people living with RLS. As research advances, we come closer and closer to finding better treatments for RLS, the cause of RLS, and hopefully soon, a cure for this condition.”

The RLS Foundation, a 501(c)(3) nonprofit organization, provides information and support for people living with RLS. The RLS Foundation’s goals are to increase awareness, to improve treatments, and, through research, to find a cure for RLS. The Foundation provides educational resources, produces the quarterly newsletter *NightWalkers*, and offers support groups. For more information, please call the toll-free number 1-877-INFO-RLS or visit the RLS Foundation's website at www.rls.org.

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