



THE BACHMANN-STRAUSS

Dystonia & Parkinson Foundation, Inc.

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Novel Mechanism Underlying the Pathophysiology of Dystonia Identified by Bachmann-Strauss Dystonia & Parkinson Foundation Grantee

Finding May Lead to Better Understanding of the Causes of Dystonia

Research funded by [The Bachmann-Strauss Dystonia & Parkinson Foundation](#) to determine the cause of an unusual speech disorder in a family living in Australia has resulted in the finding of a novel mechanism in the pathophysiology of [dystonia](#), a neurological muscle disorder that causes uncontrollable, painful spasms in one or more parts of the body and affects an estimated 500,000 people in North America alone.

[Christine Klein, MD](#), Professor of Neurology and the Schilling Professor of Clinical and Molecular Neurogenetics at the [University of Lübeck, Germany](#), and the recipient of a 2011 research grant from the Foundation, was the principal investigator of an international study group that sought to identify the gene underlying dystonia 4, (DYT4), a dominantly inherited form of spasmodic dysphonia unrelated to known dystonia genes and loci. DYT4 is an inherited movement disorder where the muscles contract and contort uncontrollably due to neurological dysfunction. Usually speech is affected first.

The speech disorder caused by DYT4 first came to the public's attention in an article published in 1985 by Neville Parker who reported on a small group of people who were all related and

lived in North Queensland, Australia. Parker wrote that those with the disorder "are able to shout and yell when emotional, have no trouble communicating after drinking alcohol and talk normally in their sleep, yet when they try to speak their voices come out only in a faint whisper. Eventually they may be unable to utter a sound when trying to talk. This whispering dysphonia may continue throughout life as an isolated feature, but more commonly is the initial presentation of a more pervasive disease with extremely varied expression." (1)

Expanding on previous research on DYT4 published in 2011(2), Dr. Klein and her team conducted genome-wide linkage analysis in 14 family members followed by genome sequencing in two individuals. Their findings were published [online](#) December 13, 2012 in the *[Annals of Neurology](#)*. (3)

With the goal of identifying the gene underlying DYT4, the research team compared the DNA of the people with the disease to 394 unrelated dystonia patients. The disease-causing gene was mapped to a small region on [chromosome 19](#), which plays a large role in many illnesses ranging from breast cancer to muscular dystrophy. Dr. Klein found that a mutation in the gene *TUBB4* caused the dystonia in the Australian family members by affecting the microtubules, fibrous, hollow rods, that function primarily to help support and shape of cells and function as routes along which organelles can move.

Commenting on the significance of the study, Dr. Klein said "the identification of DYT4 adds a new member to the growing list of inherited forms of dystonia and highlights dysfunction of neuronally expressed microtubuli as a new disease mechanism which will hopefully enable the development of new therapeutic approaches. This discovery was made possible through the careful recent examination of the DYT4 family and, based on this, corrected assignment of affected and unaffected members by my colleague Robert Wilcox from Adelaide, as well as the excellent genetics work by Katja Lohmann from our team. I would like to thank them and the entire study group for their great efforts and the DYT4 family for participating in our research and for donating samples."

Bonnie Strauss, President and Founder of [The Bachmann-Strauss Dystonia and Parkinson Foundation](#) commented, "Dr. Klein and her team have made a major breakthrough by their identification of a new mechanism that underlies dystonia and may lead to new targets and treatments for this devastating illness. Her finding is a great example of the importance of the Foundation's funding of researchers in this country and around the world."

In addition to the Foundation, the research study was funded by intramural funds from the University of Lübeck (SPP Genetics); the Hermann and Lilly Schilling Foundation; the Australian Brain Foundation and the National Health and Medical Research Council of Australia.

Study authors included scientists from University of Lübeck, Germany; Flinders Medical Centre, Adelaide, Australia; University of Bonn, Germany; University of Sydney, Sydney, Australia; Academic Medical Centre, Amsterdam, The Netherlands; Hanover University of Music, Drama and Media, Hanover, Germany; Kassel School of Medicine, Kassel, Germany; Toronto Western Hospital, University of Toronto; University Medical Centre Eppendorf, Hamburg, Germany; University of Belgrade, Belgrade, Serbia; Mount Sinai School of Medicine, New York, NY; Leiden University Medical Center, Leiden, The Netherlands and University of Groningen, Groningen, The Netherlands.

For further information about [The Bachmann-Strauss Dystonia & Parkinson Foundation](http://www.dystonia-parkinson.org), visit the Foundation's web site at www.dystonia-parkinson.org. The Bachmann-Strauss Foundation is an independent, nonprofit, 501(c)3 organization which was established in 1995 to find better treatments and cures for the movement disorders dystonia and Parkinson's disease, and to provide medical and patient information. Key among its efforts, the Foundation funds scientific and clinical research and helps to raise awareness of Parkinson's disease and dystonia among the general public and the medical community.

1. Parker N. Hereditary whispering dysphonia, *J Neurol Neurosurg Psychiatry* 1985;48:218-224 doi:10.1136/jnnp.48.3.218.
2. Wilcox RA, Winkler S, Lohmann K, Klein C. Whispering dysphonia in an Australian family (DYT4): a clinical and genetic reappraisal. *Mov Disord* 2011;26:2404-2408.
3. Katja Lohmann, Robert A Wilcox, Susen Winkler, Alfredo Ramirez, Aleksandar Rakovic, Jin-Sung Park, Björn Arns, Thora Lohnau, Justus Groen, Meike Kasten, Norbert Brüggemann, Johann Hagenah, Alexander Schmidt, Frank J Kaiser, Kishore R. Kumar, Katja Zschiedrich, Daniel Alvarez-Fischer, Eckart Altenmüller, Andreas Ferbert, Anthony E Lang, Alexander Münchau, Vladimir Kostic, Kristina Simonyan, Marc Agzarian, Laurie J Ozelius, Antonius PM Langeveld, Carolyn M Sue, Marina AJ Tijssen and Christine Klein. [Whispering dysphonia \(DYT4 dystonia\) is caused by a mutation in the TUBB4 gene](#). Accepted manuscript online: 13 DEC 2012 04:42AM EST | DOI: 10.1002/ana.23829.