Media Contact:
Hunter's Dream for a Cure
Robb Nelson, 303-909-6491
robb@huntersdream.org

Kennedy Krieger Institute
Elise Welker, Director of Communications
443-923-7330
media@kennedykrieger.org

GAME-CHANGING DISCOVERY OF GENE MUTATION THAT CAUSES STURGE-WEBER SYNDROME, PORT-WINE STAIN BIRTHMARKS OFFERS NEW HOPE

Kennedy Krieger Researchers Pinpoint Genetic Cause of Rare Disease and Common Birthmark

May 13, 2013 (Baltimore, MD) – In new findings published May 8th in the *New England Journal of Medicine*, researchers from the Kennedy Krieger Institute reveal the discovery of the cause – a genetic mutation that occurs before birth – of Sturge-Weber syndrome (SWS) and port-wine stain birthmarks. SWS is a rare disorder affecting approximately one in 20,000 births, while port-wine birthmarks are more common, affecting approximately one million individuals in the United States.

"This is a complete game changer for those with Sturge-Weber syndrome and the millions born with port-wine birthmarks," said co-senior study author, Anne Comi, M.D., Director of the Kennedy Krieger Institute's Hunter Nelson Sturge-Weber Center. "Now that we know the underlying genetic mutation responsible for both conditions, we're hopeful that we can move quickly towards targeted therapies, offering families the promise of new treatments for the first time."

This monumental medical research was made possible with funding from the Brain Vascular Malformation Consortium and ***Hunter's Dream for a Cure (HDCF)***, a Colorado based charity started by Robb & Wendy Nelson of Windsor and named after their late son Hunter who died in 2005 from a seizure caused by SWS. (www.HuntersDream.org)

"It is a very bitter and yet very sweet feeling that our funding was instrumental in determining the cause of Sturge Weber syndrome. Wendy and I are so blessed to have had the support of our family, friends, board of directors, sponsors, celebrities, volunteers and everyone that has helped us fund the ***Hunter Nelson Sturge Weber Center,*** said Robb Nelson, Co-Founder of HDCF. *"We know that for children like Hunter this means that now there is legitimate hope for treatment, early testing, etc. that will ultimately mean the difference between a good quality of life or not, and in some cases the difference between life and death."*

"It was 12 years ago that we put our faith in Dr. Comi to help Hunter & children like him and eight years ago that Hunter passed away from SWS. After Hunter passed we took the devastating pain of losing our son and renewed our commitment with the hope that other parents would not have to experience the same tragedy. This monumental research offers real hope for that to be a reality. We are eternally grateful to Dr. Comi and the entire research team, "said Wendy Nelson, Co-Founder of HDCF.

"Funding from Hunter's Dream for a Cure has been crucial in helping us make the discovery of the genetic mutation that causes SWS, said Dr. Anne Comi, Director of the Hunter Nelson Sturge-Weber Center at Kennedy Krieger Institute. "There is still a lot of work to be done, but now we have the knowledge to guide the direction of future efforts. I know that with ongoing support from HDFC, we can leverage this discovery into the development of treatments that can make Hunter's dream come true!"

SWS is a neurological and skin disorder associated with port-wine birthmarks on the face, glaucoma, seizures, intellectual impairment and weakness on one or both sides of the body. Current treatment options for children with SWS are limited, but include medications to reduce the likelihood of seizures and stroke-like episodes, eye drops and/or surgery to manage glaucoma, and physical rehabilitation.

Port-wine stain birthmarks are caused by abnormally dilated capillaries in the skin, which produce reddish to purplish discoloration. While a facial port-wine birthmark can be associated with SWS, they occur commonly in otherwise healthy

individuals. Physicians may perform several painful laser treatments to attempt to remove the port-wine birthmark in infant children, but it often reoccurs.

"This study presents a turning point for research on SWS and port-wine birthmarks," said Jonathan Pevsner, Ph.D., Director of Bioinformatics at Kennedy Krieger Institute and co-senior study author. Dr. Pevsner's laboratory found the somatic mutation (a change in DNA that occurs after conception and affects only part of the body) that causes SWS and port-wine birthmarks by performing whole genome sequencing on affected and unaffected tissue and blood samples from three individuals with SWS. They were able to identify one somatic mutation shared by all three affected samples – a nucleotide transition in gene *GNAQ* on chromosome 9q21. In a separate analysis, the researchers confirmed the finding by detecting the mutation in 23 out of 26 tissue samples from subjects with SWS and 12 out of 13 samples from subjects with isolated port-wine birthmarks. The control samples, and most of the unaffected samples, did not possess the mutation. These analyses also revealed the surprising outcome that the gene involved in SWS is the same gene implicated in uveal melanoma, a type of melanoma that occurs in the eye.

Collaborating with Kennedy Krieger scientists was Douglas Marchuk, Ph.D., and his team at Duke University Medical Center, who further illuminated *GNAQ*'s role in SWS. Within the body, *GNAQ* encodes a set of membrane proteins that ensure a set of signaling pathways within the cell are working correctly. However, in both SWS and port-wine stains, a mutation occurs in *GNAQ* that causes those sets of pathways to increase their activity, ultimately resulting in both conditions.

With the discovery of the gene and pathway involved in SWS and port-wine stains, researchers can now begin investigating drugs that selectively inhibit the implicated pathways. The link to melanoma may also influence research and lead to new directions for the treatment of both conditions in the future.

In revealing that SWS is caused by a somatic mutation, researchers have also confirmed for the first time that Sturge-Weber is not an inherited syndrome – a meaningful insight for many parents. "When a child receives a diagnosis of Sturge-Weber, parents are often filled with questions about whether they passed down the condition to their child," said Dr. Comi. "We can now definitively put those fears to rest."

This study was funded by Hunter's Dream for a Cure Foundation; and the Brain Vascular Malformation Consortium. The Brain Vascular Malformation Consortium (BVMC; U54NS065705) is a part of the National Institutes of Health (NIH) Rare Disease Clinical Research Network (RDCRN), supported through a collaboration between the NIH Office of Rare Diseases Research (ORDR) at the National Center for Advancing Translational Science (NCATS), and the National Institute of Neurological Disorders and Stroke (NINDS).

Kennedy Krieger researchers included Jonathan Pevsner, Ph.D., Anne Comi, M.D., Matthew Shirley, Ph.D., Joseph Baugher, Ph.D., and Laurence Frelin, M.S. Other study authors were Douglas Marchuk, Ph.D., Hao Tang, Ph.D., and Carol Gallione, of Duke University Medical Center; Bernard Cohen, M.D., of Johns Hopkins School of Medicine; and Paula North, M.D., Ph.D., of the Medical College of Wisconsin.

About the Hunter Nelson Sturge-Weber Center at Kennedy Krieger Institute, The Hunter Nelson Sturge-Weber Center at Kennedy Krieger Institute was founded in Baltimore, MD in 2002 through the Kennedy Krieger's University Center for Excellence in Developmental Disabilities Education, Research and Service (UCEDD) collaboration with Johns Hopkins University. The Center is dedicated to research and caring for patients with Sturge-Weber syndrome (SWS). The goals of the Center are to provide; comprehensive diagnostic evaluation and coordination of clinical services, patient, family and physician medical educational services to maximize patient function and conduct clinical and translational laboratory research aimed to improve the understanding and treatment of this disorder. Visit http://sturgeweber.kennedykrieger.org

About Hunter's Dream for a Cure, Hunter's Dream is a Colorado non-profit organization established in 2000 by Robb & Wendy Nelson in the name of their son, Hunter, who was diagnosed with SWS when he was seven months old. The foundation is dedicated to finding a cure for Sturge-Weber Syndrome and helping to assist enrichment programs for special needs kids. The foundation raises money through their fundraising events, the ***Dave Diaz-Infante Mark Schlereth Charity Golf Classic***, the ***Celebrity Hunt for a Cure*** and the ***Denim & Diamonds Gala featuring Craig Morgan and John Michael Montgomery***. The foundation was recognized in 2004 when they received the Frances Owens Communities Helping Young Children Award for demonstrating outstanding support for early childhood intervention and support programs in Colorado. In 2005 Robb & Wendy received the Pathways Achievement Award from the state of Colorado, honoring extraordinary achievements for people with disabilities. Visit www.huntersdream.org

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