UC San Diego
UC San Diego News Center

January 30, 2014 | By Scott LaFee

Scientists Discover New Genetic Forms of Neurodegeneration

In a study published in the January 31, 2014 issue of *Science*, an international team led by scientists at the University of California, San Diego School of Medicine report doubling the number of known causes for the neurodegenerative disorder known as hereditary spastic paraplegia. HSP is characterized by progressive stiffness and contraction of the lower limbs and is associated with epilepsy, cognitive impairment, blindness and other neurological features.

Over several years, working with scientific colleagues in parts of the world with relatively high rates of consanguinity or common ancestry, UC San Diego researchers recruited a cohort of more than 50 families displaying autosomal recessive HSP – the largest such cohort assembled to date. The scientists analyzed roughly 100 patients from this cohort using a technique called whole exome sequencing, which focuses on mapping key portions of the genome. They identified a genetic mutation in almost 75 percent of the cases, half of which were in genes never before linked with human disease.

“After uncovering so many novel genetic bases of HSP, we were in the unique position to investigate how these causes link together. We were able to generate an ‘HSP-ome,’ a map that included all of the new and previously described causes,” said senior author Joseph G. Gleeson, MD, Howard Hughes Medical Institute investigator, professor in the UC San Diego departments of Neurosciences and Pediatrics and at Rady Children’s Hospital-San Diego, a research affiliate of UC San Diego.

The HSP-ome helped researchers locate and validate even more genetic mutations in their patients, and indicated key biological pathways underlying HSP. The researchers were also interested in understanding how HSP relates to other groups of disorders. They found that the HSP-ome links HSP to other more common neurodegenerative disorders, such as Alzheimer’s disease and amyotrophic lateral sclerosis.

“Knowing the biological processes underlying neurodegenerative disorders is seminal to driving future scientific studies that aim to uncover the exact mechanisms implicated in common neurodegenerative diseases, and to indicate the path toward development of effective treatments,” said Gleeson.

“I believe this study is important for the neurodegenerative research community,” said co-lead author Gaia Novarino, PhD, a post-doctoral scholar in Gleeson’s lab. “But more broadly, it offers an illustrative example of how, by utilizing genomics in specific patient populations, and then building an ‘interactome,’ we greatly expand knowledge around unknown causes of disease.”

“This is very exciting since identifying the biological processes in neurological disorders is the first step toward the development of new treatments,” agreed co-lead author Ali G. Fenstermaker. “We identified several promising targets for development of new treatments.”

Co-authors include Maha S. Zaki, Ghada M.H. Abdel-Salam, Mahmood Y. Issa and Hisham Megahed, National Research Centre, Cairo; Matan Hofree, UCSD Departments of Medicine and Engineering and Neurosciences; Jennifer L. Silhavy, Andrew D. Heiberg, Mostafa Abdellatef, Basak Rosti, Eric Scott, Massimo Mascaro, Jana Schroth, Emily G. Spender, Rasim O. Rosti, Naiara Akizu, Keith A. Vaux and Alice A. Koh, Howard Hughes Medical Institute; Lobna Mansour, Iman Gamal El Din Mahmoud and Laila Selim, Cairo University Children’s Hospital; Amira Masri, University of Jordan; Hulya Kayserili, Istanbul University; Jumana Y. Al-Aama, King Abdulaziz University, Saudi Arabia; Ariana Karminejad and Bita Bozorgmehri, Kariminejad-Najmabadi Pathology and Genetics Center, Iran; Majdi Kara, Tripoli Children’s Hospital, Libya; Bulent Kara, Kocaeli University, Turkey; Tawfeq Ben-Omran, Hamad Medical Corporation, Qatar; Faezeh Mojahedi, Mashhad Medical Genetic Counseling Center, Iran; Naima Bouslam, Ahmed Bouhouche and Ali Benomar, University Mohammed C Souissi, Morocco; Sylvain Hanein, Laure Raymond and Sylvie Forlani, Centre de Recherche de l’Institut du Cerveau et de la Moelle Epiniere; Nabil Shehata, Saudi German Hospital, Saudi Arabia; Nasir Al-Allawi, University of Dohuk, Iraq; P.S. Bindu, NIMHANS, India; Matloob Azam, Wah Medical College, Pakistan; Murat Gunel, Ahmet Caglayan and Kaya Bilguvar, Yale University School of Medicine; Alexandra Durr, Centre de Recherche de l’Institut up Cerveau et de la Moelle Epiniere and APHP, Federation de Genetique, France; Alexis Brice, Centre de Recherche de l’Institut up Cerveau et de la Moelle Epiniere, APHP, Federation de Genetique and Institut du Cerveau et de la Moelle Epiniere, France; Giovanni Stevanin, Centre de Recherche de l’Institut up Cerveau et de la Moelle Epiniere, APHP, Federation de Genetique and Institut du Cerveau et de la Moelle Epiniere, France; Stacy Gabriel, Broad Institute of Harvard and Massachusetts Institute of Technology, and Trey Ideker, UCSD Departments of Medicine and Engineering and Neurosciences.

Funding for this research came, in part, from the Deutsche Forschungsgemeinschaft, the BBRF, National Institutes of Health grants R01NS041537, R01NS048453, R01NS052455, P01HD070494 and P30NS047101, the French National Agency for Research, the Verum Foundation, the European Union, Fondation Roger de Spoelberch, Investissements d'avenir and the Princess Al Jawhara Center of Excellence in Research of Hereditary Disorders.
