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New genetic forms of neurodegeneration discovered

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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."

More information: "Exome Sequencing Links Corticospinal Motor Neuron Disease to Common Neurodegenerative Disorders," by G. Novarino et al. *Science*, 2014.

Provided by University of California - San Diego