Researchers discover new genetic brain disorder in humans

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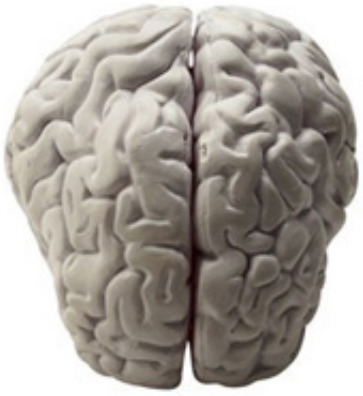

A newly identified genetic disorder associated with degeneration of the central and peripheral nervous systems in humans, along with the genetic cause, is reported in the April 24, 2014 issue of *Cell*.

The findings were generated by two independent but collaborative scientific teams, one based primarily at Baylor College of Medicine and the Austrian Academy of Sciences, the other at the University of California, San Diego School of Medicine, the Academic Medical Center (AMC) in the Netherlands and the Yale University School of Medicine.

By performing DNA sequencing of more than 4,000 families affected

by neurological problems, the two research teams independently discovered that a disease marked by reduced brain size and sensory and motor defects is caused by a mutation in a gene called CLP1, which is known to regulate tRNA metabolism in cells. Insights into this rare disorder, the researchers said, may have important implications for the future treatment of more common neurological conditions.

"What we found particularly striking, when considering the two studies together, is that this is not a condition that we would have been able to separate from other similar disorders based purely on patient symptoms or clinical features", said 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. "Once we had the gene spotted in these total of seven families, then we could see the common features. It is the opposite way that doctors have defined diseases, but represents a transformation in the way that medicine is practiced."

Each child tested was affected by undiagnosed neurological problems. All of the children were discovered to carry a mutation in the CLP1 gene and displayed the same symptoms, such as brain malformations, intellectual disabilities, seizures and sensory and motor defects. A similar pattern emerged in both studies, one led by Gleeson, with Murat Gunel, MD, of the Yale University School of Medicine and Frank Baas, PhD, of the Academic Medical Center in the Netherlands, and the other by Josef Penninger and Javier Martinez of the Austrian Academy of Sciences, teamed with James R. Lupski, MD, PhD, of the Baylor College of Medicine.

"Knowing fundamental pathways that regulate the degeneration of neurons should allow us to define new pathways that, when modulated, might help us to protect motor neurons from dying, such as in Lou

Gehrig's disease," said Penninger, scientific director of the Institute of Molecular Biotechnology of the Austrian Academy of Sciences.

The CLP1 protein plays an important role in generating mature, functional molecules called transfer RNAs (tRNAs), which shuttle amino acids to cellular subunits called ribosomes for assembly into proteins. Mutations affecting molecules involved in producing tRNAs have been implicated in human neurological disorders, such as pontocerebellar hypoplasia (PCH), a currently incurable neurodegenerative disease affecting children. Although CLP1 mutations have been linked to neuronal death and motor defects in mice, the role of CLP1 in human disease was not known until now.

These scientists performed DNA sequencing on children with neurological problems. Seven out of the more than 4,000 families studied shared an identical CLP1 mutation, which was associated with motor defects, speech impairments, seizures, brain atrophy and neuronal death.

Bass at the AMC said the neurological condition represents a new form of PCH. "Identification of yet another genetic cause for this neurodegenerative disorder will allow for better genetic testing and counseling to families with an affected child," he said.

In a published paper last year, Gleeson and colleagues identified a different gene mutation for a particularly severe form of PCH, and reported early evidence that a nutritional supplement might one day be able to prevent or reverse the condition.

More information: *Cell*, Karaca et al.: "Human CLP1 mutations alter tRNA biogenesis affecting both peripheral and central nervous system function." dx.doi.org/10.1016/j.cell.2014.02.058

Cell, Schaffer et al.: "CLP1 Founder Mutation Links tRNA Splicing and Maturation to Cerebellar Development and Neurodegeneration." dx.doi.org/10.1016/j.cell.2014.03.049