UCSD Researchers Link Novel Mutated Gene to Mental Retardation and Imbalance Syndrome

May 08, 2006 |

Researchers at the University of California, San Diego School of Medicine have identified a genetic cause for a form of pediatric brain malformation involving the cerebellum. Future research based on these findings could lead to ways of preventing or treating children with Joubert Syndrome Related Disorder (JSRD.)

The research team, directed by Joseph Gleeson, M.D., Director of the Neurogenetics Laboratory at the UCSD School of Medicine and associate professor in the Department of Neurosciences, have identified a new gene that, when mutated, leads to JSRD. Their findings will be published on-line May 7 in advance of publication in the journal *Nature Genetics*.

JSRD is a group of neurodevelopmental syndromes marked by absence of the middle part of the cerebellum called the vermis, along with features including poor balance, jerky eye movements, mental retardation and autism. The most consistent feature seen in children affected with JSRD is a striking finding on brain MRI called the "molar-tooth sign," in which the base of the brain takes on the appearance of a tooth. A subset of JSRD patients also displays disease in other body organs including the retina, kidneys and liver.

The discovery of the new gene linked to JSRD was found in collaboration with scientists at the Mendel Institute in Rome, under the direction of Enza Maria Valente. The researchers studied a large family from Sardinia, Italy, with several members exhibiting the disease. Within the family, in which the parents were second cousins, the scientists discovered a new genetic interval and the presence of the CEP290 (Centrosome-associated protein 290) gene. The research teams identified inactivating mutations in CEP290 in this family and mutations were also identified in families with similar diseases in Turkey, the Palestinian region of Israel and Pakistan. This gene has not previously been implicated in human disease, and encodes a novel protein, previously identified as a centrosomal-associated protein, but with unknown function.

Once the mutations were identified, the group set out to understand the role of the protein in development of the human cerebellum. They found that the gene was produced predominantly in the population of neurons in the brain called cerebellar granule neurons. They also discovered

specific protein targets suggesting that the gene may control cell division in the cerebellum during the human development, which would account for the cerebellar defect seen in these patients.

"The results are interesting, because they connect JSRD with other diseases in which retina, kidney and liver are diseased," said Gleeson. These diseases, including recessive kidney cyst disease, Senior-Loken, Bardet-Biedl and Meckel syndromes, are caused by genes that encode proteins localized to ciliated structures or the centrosome. "The data suggests that JSRD may fall into these groups of conditions, although the exact mechanism of how the CEP290 protein regulates cerebellar development remains unknown."

In 2004, Gleeson and his colleagues – along with scientists at Harvard University – discovered mutations in the AH1 gene found on chromosome 6 DNA. The gene is responsible for the most common of three known forms of Joubert Syndrome and was the first genetic defect clearly associated with the disorder.

Additional contributors to the current study include Jennifer Silhavy, Suguna Krishnaswami, Madeline Lancaster and Carrie Louie from the Gleeson lab; Francesco Brancati, Giuseppe Barrano, Maro Castori, Emanuele Bellacchio and Bruno Dallapiccola from the Valente Lab; Eugen Bolshauser, Children's University Hospital in Zurich, Switzerland; Loredana Boccone, Ospedale Microcitemico, Cagliari, Italy; Lihadh Al-Gazali, United Emirates University; Elisa Fazzi, University of Pavia, Italy; Enrico Bertini, Bambino Gesu Hospital in Rome and the International JSRD Study Group.

Funding for this research was provided by grants from the U.S. National Institute of Neurological Disease and Stroke, the Italian Ministry of Health, the Fonazione Pierfranco e Luisa Mariana ONLUS, the March of Dimes, the Simons Foundation and the Burroughs Wellcome Fund Award in Translational Research.

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