Researchers Identify Gene Responsible for Rare Childhood Disease

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The chromosomal abnormality that causes a rare, but often fatal, disorder that affects infants has been identified by researchers at the University of California, San Diego School of Medicine, who happened to treat two young children with the disease in San Diego – two of perhaps a dozen children in the entire country diagnosed with the disorder.

Congenital Tufting Enteropathy (CTE) is a rare, congenital disorder that causes changes in the intestines of children that lead to severe diarrhea, the inability to consume food or absorb nutrition, and subsequent growth failure. Children with CTE are dependent on receiving nutrition through an IV (or catheter in a vein), which can result in many medical problems and even early death. Despite its grave complications, there has been little understanding about what causes this devastating "orphan" disease.

Two of those children live in the San Diego area where they were being treated at Rady Children's Hospital. But it was a second strange coincidence that led the study's principal investigator Mamata Sivagnanam, M.D., assistant professor of clinical pediatrics in the Division of Pediatric Gastroenterology, Hepatology and Nutrition at UCSD's School of Medicine and Rady Children's Hospital in San Diego, to discover the gene that is altered in patients with CTE.

The discovery will be published as a cover story of the August issue of the journal *Gastroenterology,* and is currently available on line.

Sivagnanam and her colleagues were treating a young infant with severe diarrhea in the neonatal intensive care unit at Rady Children's Hospital and diagnosed him with CTE. At the same time, they were treating this rare disorder in another child, who was 1-1/2 years old at the time, and noticed that they both had the same, uncommon last name.

"It turned out that these two children were what is called double second cousins," Sivagnanam said, meaning that the two mothers are first cousins, and so are the two fathers – sharing a common set of grandparents. "We suspected that this was a heritable disease, but these two

families – unknown to one another – each had a child with CTE. This unique familial relationship enabled us to isolate the chromosome mutated in the disorder."

Using genetic technology that can determine small variations in the genetic code within a person's DNA sequence known as single nucleotide polymorphisms (or SNPs, pronounced "snips"), the researchers determined that mutation of a molecule known as the Epithelial Cell Adhesion Molecule or EpCAM is the cause of CTE.

"We hope that this information will allow us to not only understand what causes this disease, but eventually lead to further advances in its diagnosis and treatment," Sivagnanam said. "By understanding the role of EpCAM in the intestine, it may also lead to better understanding of diseases such as colon cancer and inflammatory bowel disease."

Dr. Sivagnanam's research mentor is Hal M. Hoffman, M.D., an associate professor of medicine and pediatrics at UCSD who also discovered a protein implicated to two other rare disorders: familial cold autoinflammatory syndrome (FCAS), in which affected people develop rashes and other symptoms when exposed to cold air, and Muckle-Wells syndrome (MWS), which causes deafness as well as periodic fevers.

Additional contributors to the study include Richard D. Kolodner, M.D., Ludwig Institute of Cancer Research, UCSD Department of Medicine and Moores UCSD Cancer Center; James L. Mueller, Ludwig Institute of Cancer Research and UCSD Department of Pediatrics; Hane Lee, Zugen Chen and Stanley F. Nelson, UCLA Department of Genetics; Dan Turner, Stanley H. Zlotkin and Paul B. Pencharz, Bo-Yee Ngan, The Hospital for Sick Children, Toronto; Ondrej Libiger and Nicholas J. Schork, Ph.D., Scripps Genomic Medicine, Scripps Health and The Scripps Research Institute, La Jolla; and Joel E. Lavine, M.D., and Sharon Taylor, M.D., UCSD Department of Pediatrics and Rady Children's Hospital, San Diego.

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