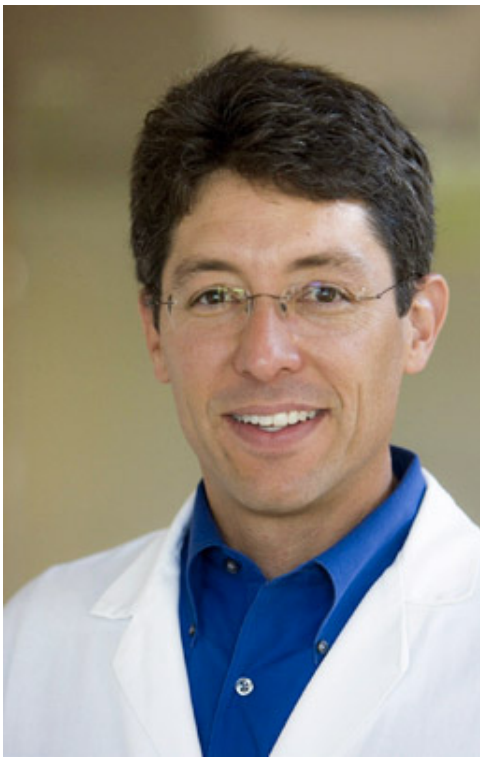
UC San Diego
UC San Diego News Center

June 13, 2012 | By Scott LaFee

Clarity Begins at Exome

Sequencing Protein-making Part of Genome Can Change Diagnosis and Patient Care

In the June 13 issue of *Science Translational Medicine*, an international team led by researchers from the University of California, San Diego School of Medicine reports that the new technology of exome sequencing is not only a promising method for identifying disease-causing genes, but may also improve diagnoses and guide individual patient care.



Joseph G. Gleeson, MD

In exome sequencing, researchers selectively and simultaneously target and map all of the portions of the genome where exons reside. Exons are short, critical sequences of DNA in genes that are translated into proteins – the biological workhorses involved in virtually every cellular function, plus various structural or mechanical duties.

The researchers, headed by principal investigator Joseph G. Gleeson, MD, professor of neurosciences and pediatrics at UC San Diego and Rady Children's Hospital-San Diego, sequenced the exomes of 118 patients who had been diagnosed with specific neurodevelopmental diseases. In each of the cases, all known genetic causes of their disease had been previously excluded.

Not surprisingly, the scientists found that exome sequencing newly identified numerous disease-causing genes, including the identification of the *EXOC8* gene as a cause of Joubert syndrome, a condition affecting the developing cerebellum, and *GFM2* as a cause for a condition that results in a small brain combined with pediatric diabetes.

More surprising, the researchers discovered that in approximately 10 percent of cases, exome sequencing led to the identification of a *known* disease-causing gene, prompting a change in diagnosis and care for some patients.

“Initially, we were surprised to find mutations in genes already known to cause human disease, because we had previously excluded the known causes based upon the patient diagnosis,” said Gleeson. “When we went back to the patients to figure out what had happened, we determined that, in each case, the original diagnosis did not agree with the genetic diagnosis. This happened in about 10 percent of the cases we studied, even though the patients had been diagnosed according to standard clinical practice.”

In each case, the researchers determined that the genetic diagnosis was fully correct, and by careful review of the patient record, determined that the original diagnosis was incorrect. “If we extrapolate these results to the general population seen in these clinics, we can infer that a large number of patients could possibly have their diagnosis and treatment modified by advanced genetic testing.”

Gleeson said the reason for these inconsistencies were manifold, but did not reflect errors in medical diagnosis – at least none that the research team could identify. Instead, he said the differences highlight the inherent difficulty of achieving specific diagnoses, particularly given the complexities of brain development and function.

Tracy Dixon-Salazar, PhD, a member of Gleeson’s lab and first author of the study, said the findings provide proof that exome sequencing in the clinic can be a valuable tool for diagnosing disease, especially in patients like those with neurodevelopmental disorders where the prognosis is poor and treatments are limited.

Co-authors are Jennifer L. Silhavy, Jana Schroth, Stephanie Bielas, Ashleigh E. Schaffer, Jesus Olvera, Kiley J. Hill, Adrienne Collazo, Ali G. Fenstermaker, Gaia Navarino and Naiara Akizu, Howard Hughes Medical Institute, UC San Diego Institute for Genomic Medicine, Rady Children’s Hospital; Nitin Udpa and Vineet Bafna, Department of Computer Sciences, School of Engineering, UC San Diego; Maha S. Zaki and Ghada H. Abdel-Salam, Clinical Genetics Department, Human Genetics and Genome Research Division, National Research Center, Cairo, Egypt; Lobna A. Mansour, Laila Selim and Sawsan Abdel-Hadi, Cairo University Children’s Hospital; Naima Marzouki, Laboratoire Genetique Moleculaire, El Razi University Hospital, Marrakech, Morocco; Tawfeg Ben-Omran, Clinical and Metabolic Genetics Division, Department of Pediatrics, Hamad Medical Corporation, Doha, Qatar; Nouriya A. Al-Saana, Department of Pediatrics, Dhahran Health Center, Saudi Aramco Corporation, Dhahan, KSA; F. Mujgan Sonmez and Figen Celep, Child Neurology Department, Medical School of Karaderiz Technical University, Trabzon, Turkey; Matloob Azam, Department of Pediatrics and Child Neurology, Wah Medical College, Wah Cantt, Pakistan; Kiran V. Garimella, Carrie Sougnez, Carsten Russ and Stacey B. Gabriel, Broad Institute of Massachusetts Institute of Technology and Harvard.

Funding for this research came, in part, from the Howard Hughes Medical Institute; the National Institute of Neurological Disorders and Stroke grants R01N5041537, R01NS048453 and R01NS052455; National Human Genome Research Institute grants P01HD070494 and

US4HG003067; National Institute on Alcohol Abuse and Alcoholism/Center for Inherited Disease Research grant N01-HG-65403; and National Science Foundation grants III-081905 and CCF-1115206.
