

Clarity begins at exome: Sequencing protein-making part of genome can change diagnosis and patient care

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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.

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.

Provided by University of California - San Diego

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