MedicalXpress

DNA test identifies genetic causes of severe fetal and newborn illness

October 8 2020

Credit: CC0 Public Domain

A new study by University of California researchers shows the promise of high-throughput DNA-sequencing technologies to improve prenatal diagnosis and pregnancy outcomes for women who have experienced an abnormal prenatal ultrasound.

In the UCSF-led study, scientists used a technique called exome

sequencing to identify genetic diseases as the underlying cause in 37 of 127 cases of nonimmune hydrops fetalis (NIHF), a life-threatening condition in which the fetus is overloaded with fluid. The study was published online Oct. 7, 2020, in *The New England Journal of Medicine (NEJM)*.

Corresponding author Teresa Sparks, MD, MAS, a UCSF assistant professor in the Department of Obstetrics, Gynecology & Reproductive Sciences, led the study with senior study author Mary Norton, MD, a professor in the same department. "The cause of most cases of NIHF is not identified with standard testing, but when we apply exome sequencing, we find a genetic diagnosis in nearly 30 percent of cases of previously unknown cause," Sparks said.

NIHF affects about one in every 1,700 to 3,000 pregnancies in the United States and is associated with high risks of stillbirth, preterm birth, neonatal death and other complications. Although NIHF often leads to death, identifying the precise genetic cause is critical, as associated outcomes vary widely in severity.

NIHF can be a manifestation of many genetic diseases, but evidence of abnormal fluid accumulation in the fetus detected through an ultrasound exam—whether it occurs under the skin, in the abdomen, or around the heart or lungs—does not pinpoint an underlying cause.

Participants in the *NEJM* study were referred from throughout the United States after NIHF was identified with prenatal ultrasound but no underlying genetic disease was found using long established methods for detecting genetic abnormalities. These traditional genetic tests—karyotype and chromosomal microarray analysis—detect large abnormalities in chromosomes, not disorders caused by a defect in a single gene as are identified with exome sequencing.

Exome sequencing is the complete spelling out of the genetic code for DNA segments within the genome that serves as the blueprints for proteins. This has become possible to perform quickly and accurately in recent years, thanks to the continual refinement of technology that can sequence DNA strands that are thousands of nucleotide building blocks long, often in a massively parallel manner that helps ensure accurate results. Exome sequencing can identify even the smallest mutations, such as a change in a single building-block nucleotide base pair.

Importantly, many of the disorders identified in the study have not previously been reported in association with NIHF, so the findings broaden knowledge of genetic diseases that can present with the condition. Among the most common of 37 genetic disorders identified in the *NEJM* study were 11 cases affecting a key intracellular signaling pathway called RAS-MAPK, four cases of inborn errors of metabolism, four cases of musculoskeletal disorders, and three cases each of lymphatic, neurodevelopmental, cardiovascular and blood disorders. Many of these diagnoses would also have been missed by commercial gene panels, Sparks said.

Most mutations identified in the study newly arose in the fetus, but several were inherited, with the potential to affect future pregnancies with the same biologic mother or father.

"There is a very wide range in genetic diagnoses underlying NIHF, and identifying the diagnosis is essential for families and healthcare providers," Sparks said. "With advanced genetic testing, there is much more we can discover for families to help them understand the situation, for obstetricians and neonatologists to better take care of the pregnancy and anticipate the needs of the newborn, and ultimately to guide the development of novel prenatal management strategies such as in-utero therapies to improve health outcomes over the long term."

For some of the genetic disorders identified in the study, prenatal interventions that can improve or save lives already have been identified. For example, genetic causes of anemia in the fetus may be closely monitored, and the fetus may receive a blood transfusion if needed.

Similarly, for some of the inborn errors of metabolism identified in the study, enzyme therapies already are available after birth. Early diagnosis and treatment of these metabolic disorders leads to better outcomes. A co-author of the *NEJM* study, Tippi MacKenzie, MD, a professor with the UCSF Department of Surgery, is investigating in utero treatments for specific genetic disorders underlying NIHF in a new clinical trial. Sparks, Norton, and co-authors are also pursuing further investigations to identify additional genomic abnormalities underlying NIHF for the cases that remain unsolved.

More information: Teresa N. Sparks et al, Exome Sequencing for Prenatal Diagnosis in Nonimmune Hydrops Fetalis, *New England Journal of Medicine* (2020). DOI: 10.1056/NEJMoa2023643

Provided by University of California, San Francisco