THE AMERICAN SOCIETY OF HUMAN GENETICS

NEWS

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DNA sequencing of infants and children with anatomical defects of unknown causes: challenges and opportunities

A presentation at the American Society of Human Genetics 2012 meeting today (Nov. 6) updated genetics experts about a one-year-old research initiative that brought together researchers, clinicians and policy experts to tackle the challenges of incorporating new genomic technologies into the clinical care of newborns, infants and children with anatomical defects whose causes are unknown.

Among the challenges is interpreting how variations in patients' DNA cause or contribute to their medical problems, said Duke University Assistant Professor of Pediatrics Erica E. Davis, Ph.D., who presented the update and is based in the Center for Human Disease Modeling in the university's medical center.

In 2011, the center founded the Duke Task Force for Neonatal Genomics to act as a nucleus for a group of physicians and scientists with the diverse skills sets needed to bridge genetics, genomics, cell biology, ethics and clinical investigation and to offer a "360 degree" view of challenging clinical pediatric cases, Dr. Davis said.

"Strikingly, preliminary analysis of the task force's first year of work has suggested definitive or strong candidate diagnoses in some 90% of the recruited cases," she noted.

During its first year, the task force screened over 150 newborns, infants and children, enrolled 20 patients and developed the capacity to enroll about 100 patients each year. "Our patients come from the Duke fetal diagnostic center, the Duke intensive care nursery and various pediatric specialty clinics," she said.

In one child with severe epilepsy, the task force used sequencing of the protein-coding regions of the genome (about 2% of the entire human genome) to identify a broken gene that impairs the ability of sodium to move in and out of cells.

"We determined that the child's condition was caused by a new mutation in a gene named *SCN2A*," Dr. Davis said. This approach was also used to help diagnose genetic disorders in babies with a variety of conditions including congenital muscle weakness, fluid in the brain and kidney cysts.

(more)

"The task force's goal is to create a model of how and when genetic sequencing should be a first-tier diagnostic tool to inform and guide clinical management and treatment of young children with unexplained congenital defects," she said.

"By sequencing the DNA of these children early in life, clinicians can make use of personalized genomic information that, in combination with all of the other tools doctors have at their disposal, can inform patient management and potentially improve outcomes.

"We have a large interdisciplinary team that includes researchers, clinicians and policy scholars. What binds us together are the shared goals of using new genetic technologies to improve the health of these patients and sharing as much information as we can with their families," Dr. Davis added.

Dr. Davis described the task force's interdisciplinary approach; how it recruits patients and produces and analyzes data; and how it keeps families and their physicians informed before, during and after DNA sequencing. The latter, she said, includes "our evolving and inclusive approach to returning primary and secondary genomic findings to clinicians and family members."

Once DNA variants or mutations suspected to cause disease are identified by sequencing patients' DNA, the task force then attempts to determine what those variants actually do by measuring their effects in animal models, most notably zebra fish. "We can't be completely certain that we have found 'the gene or genes' until we understand what a variant does in a living cell," she said.

The task force focuses on keeping participating families informed and engaged because, "by the time they enroll in our study, our patients and their parents have usually been on a long 'diagnostic odyssey' and have come up empty," Dr. Davis said.

"We want to do whatever we can to change that. We don't want to be one more source of frustration and disappointment to them. We can't offer any guarantees, but we want them to think of us as partners. We are fully invested in trying to find answers and make their lives and their children's lives better if we can," she added.

Duke's Center for Human Disease Modeling was established in late 2009 under the leadership of Nicholas Katsanis, Ph.D., Jean and George Brumley Jr., M.D., Professor of Developmental Biology, and Professor of Pediatrics and Cell Biology.

The researchers' abstract is titled, "Multidisciplinary and Translational Task Force for Neonatal Genomics."

About ASHG

The American Society of Human Genetics is the primary professional membership organization for nearly 8,000 human genetics specialists worldwide. The ASHG Annual Meeting is the world's largest gathering of human genetics professionals and a forum for renowned experts in the field.

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