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Exome reanalysis can improve diagnostic rate for Mendelian disorders

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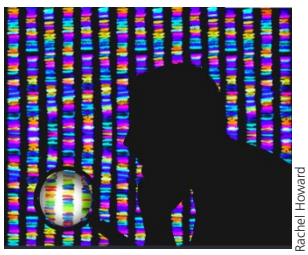

Rachel Howard

A research team at Stanford University reports reanalysis of data and provision of diagnoses for 4 out of 40 patients who had previously had nondiagnostic results returned from clinical exome sequencing. The study highlights the benefit of revisiting sequence data as analytical techniques improve and knowledge of gene–disease associations increases. The researchers, from a pediatric genetic clinic, recruited patients with suspected Mendelian disorders who had been given a nondiagnostic finding after exome sequence analysis within the previous two to three years. After combining improved analysis software and information gleaned from the current literature, they definitively diagnosed patients who had quite recently been told no genetic cause for their symptoms could be identified. In one case, a patient was diagnosed with Wiedemann-Steiner syndrome (WDSTS) caused by a mutation in *KMT2A*. The first report to link the *KMT2A* gene to WDSTS was published only two weeks after the nondiagnostic result had been returned. The researchers point out that had the clinical exome been ordered a month later, the exome data could have provided a diagnosis. Instead, three years after the exome sequence test, the patient remained undiagnosed. This study demonstrates the potential need for periodic reevaluation of nondiagnostic exomes. Given the rate of increase in the number of disorders with a known molecular basis (an average of 266 entries per year in the Online Mendelian Inheritance in Man database), the authors also point to an urgent need to speed the rate of inclusion of the primary literature into structured clinical databases. *—Karyn Hede, News Editor*

Method could broaden prenatal screening for trisomies

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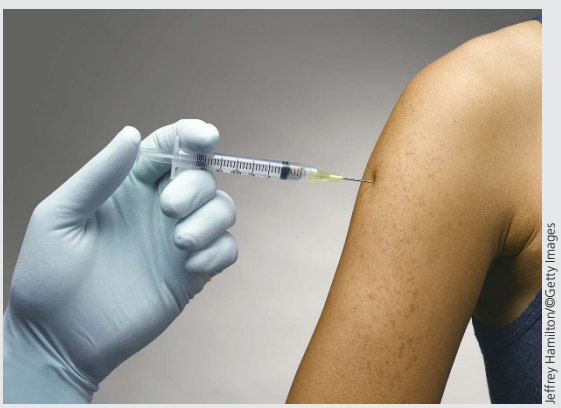
Rachel Howard

Current methods for prenatal testing using cell-free DNA (cfDNA) screen for only the three most common trisomies—21, 18, and 13—ignoring the more rare forms. In this issue, a Lausanne, Switzerland-based research group reports a method that could expand the utility of cell-free DNA (cfDNA) for detection of prenatal chromosomal abnormalities. The method, developed by a commercial testing service, incorporates not only rare autosomal trisomies (RATs) but also sex-chromosome anomalies (SCAs) and disease-causing copy-number variations (CNVs). Testing an extended range of anomalies in a series of 6,388 consecutive singleton pregnancies revealed 258 (4%) of samples to be abnormal or likely abnormal. The anomalies consisted of 119 common trisomies, 53 SCAs, 50 RATs, and 36 CNVs. Two false-negative results were caused by low fetal fraction and true fetal mosaicism. On the basis of these data, the investigators suggest that cfDNA screening be extended to include detection of RATs and recurring deletion/duplication CNVs. However, they caution that CNV screening should be limited to a list of well-characterized genomic disorders, as clinically actionable data on nonrecurring CNVs is unreliable. The authors argue that detection of RATs is clinically justifiable because the accuracy of the new method approaches that of the current method for detecting common trisomies. Registry data, the authors point out, show that these clinically relevant anomalies are not currently being detected. *—Karyn Hede, News Editor*

NEWS BRIEFS

CRISPR technology moving toward human gene therapy

Researchers at the University of Pennsylvania are reporting they have used a CRISPR/Cas9-mediated gene targeting system to "cure" hemophilia B, caused by mutations in the blood clotting factor IX gene, in mice. Their research, presented at the American Society of Hematology annual meeting in December 2016, included data collected over four months posttreatment. The proof-of-concept research demonstrates the potential of the new approach to gene therapy but still relies on adeno-associated viral vectors, which come with their own risks, to deliver the functional components. Lili Wang, research associate professor in the Penn Gene Therapy Program (GTP), and James M Wilson, professor of medicine and GTP director, led the research. The method specifically targets a region of the mouse factor IX gene and contains a partial human factor IX complementary DNA sequence. The researchers say the vector could potentially



Jeffrey Hamilton/©Getty Images

NEWS BRIEFS *(continued)*

be used in patients with any mutations in the factor IX gene: The announcement comes as Penn researchers are poised to begin the first human clinical trials in the United States to use CRISPR gene-editing technology. A Penn-led team will be manufacturing T cells edited to treat cancer patients in a trial funded by the new Parker Institute for Cancer Immunotherapy. This phase I safety trial of 18 patients with several types of cancer will attempt to target cancer cells for immune system destruction. *—Karyn Hede, News Editor*

Ancient tree duplicated genes to survive, outlasting dinosaurs

Fossil hunters cracking open rocks that harbor leafy remains of ancient seabeds would be hard-pressed to distinguish fossilized ginkgo leaves from those of their living relatives, now dispersed globally. The ancient tree, which lived alongside dinosaurs during the Jurassic period, has changed little since then. Recently, the hardy survivor's genome was finally

Anders Sandberg/Wikimedia Commons

sequenced, revealing secrets behind the evolution of seed plants. Wenbin Chen from the Beijing Genomics Institute led the tedious effort to complete the enormous 10.61 GB genome (three times as large as the genome of us humans!) with its 41,840 annotated genes and many repeated sequences, including long terminal repeat retrotransposons, which are unusually prevalent. The researchers concluded that the whole genome may have been duplicated at some point, possibly twice. The newly completed genome, published November 2016 in the journal *GigaScience*, will assist in the assembly and annotation of the published genome drafts of pines and other gymnosperms. In addition, the research team focused on evidence of expansion of gene families that provide defense against pests and disease. Widely known for its longevity and hardiness, the gingko survived periods of glaciation in China that killed many other species as well as, of course, the extreme environmental upheavals that finished off the dinosaurs. The ginkgo's arsenal of weapons includes synthesis of chemicals that directly fight insect damage and indirectly target insects by attracting enemies of plant-eating insects. These findings indicate that having multiple genetic strategies, including expansion of gene families, higher doses of specific genes, and a variety of defensive genes, might contribute to the tree's longevity and resilience. *—Karyn Hede, News Editor*