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Exome reanalysis can improve diagnostic rate for Mendelian disorders

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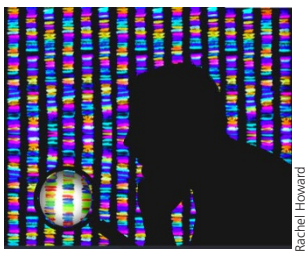

Rachel Howard

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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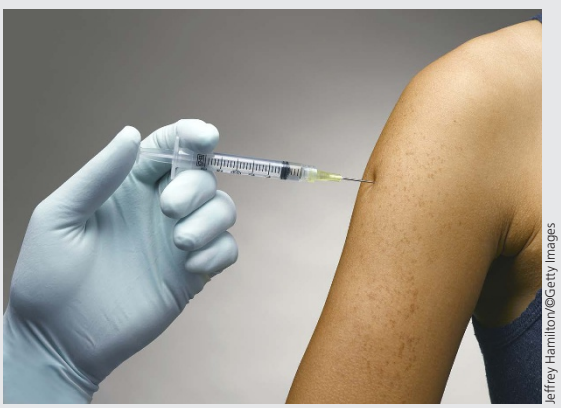
Rachel Howard

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



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