Cutting-Edge DNA Sequencing Used to Diagnose Unknown Disease

Miriam E. Tucker | Mar 11, 2013

Deoxyribonucleic acid sequencing is emerging as a clinical tool to help diagnose mystery diseases, investigators report.

"If physicians have cases for which they've done everything they know what to do and they really need a diagnosis, this is an alternative now," Howard Jacob, PhD, from the Medical College of Wisconsin in Milwaukee, told *Medscape Medical News*.

Dr. Jacob said that at his center, the use of genomic sequencing ups the odds of finding a diagnosis by 3- to 6-fold.

Presenting at the opening session at the Future of Genomic Medicine (FoGM) VI conference in La Jolla, California, Dr. Jacob and other experts said they envision a future where whole-genome sequencing will be routinely performed on every individual at birth.

The meeting, which brought together thought leaders in the field, was co-sponsored by Scripps Translational Science Institute and the American Association for the Advancement of Science.

In the more near-term, however, the speakers suggested whole-genome and exome sequencing are viable options for helping patients and families who suffer from illnesses for which all the usual tests have failed to find a diagnosis.

Dr. Jacobs pointed out that while these approaches show promise, even with gene sequencing, only about a quarter of cases end up with a diagnosis.

"The biggest problem," he said, "is that we need more genomes sequenced and more work on studying potential variants."

Gene testing, Dr. Jacobs added, will not replace clinical assessment. "Gene testing alone will never be enough. Gene testing, sequencing is another lab value to help."

It's not a question of if this is going to be a part of medical practice; it's a question of when.

William Gahl, MD, clinical director of the National Human Genome Research Institute in Bethesda, Maryland, said he agrees. "It's really important to phenotype patients. If looking for specific genes, we need to know all the characteristics and clinical manifestations very well," he told *Medscape Medical News.*

Dr. Gahl directs the National Institutes of Health's Undiagnosed Diseases Program (UDP), a project that aims to help patients and families find answers when all the usual medical testing fails.

As previously reported by *Medscape*, the UDP uses extensive phenotypic investigation on selected patients as well as single-gene, whole-genome and exome sequencing to try to identify causes for a wide range of rare diseases and variants.

The UDP was first launched in May 2008 with a $3.5 million budget. Since then, all its work has taken place on the NIH campus in Bethesda. In July 2012, the program received $145 million in funding over the next decade to expand to 5 to 7 additional centers around the country.

Physicians refer patients to the center via letter, along with medical records. Of approximately 2700 applications received, about 630 have been accepted into the program. Of those, 39% are children. About half of the cases are neurological, including some that turn out to be mitochondrial. Many are complex pediatric genetic disorders, Dr. Gahl said.

Phenotype First

Patients undergo extensive phenotypic investigation before any sequencing is done. In 10 to 20% of cases, a diagnosis is made without sequencing.

About 5% of participants receive targeted sequencing and about half get exome sequencing. The UDP hasn't used whole-genome sequencing yet, said Dr. Gahl.

In addition to helping individual patients and families, another of the UDP's goals is to discover new diseases that might provide insight into human physiology as well as into other related diseases.

In one such case evaluated at UDP, 5 siblings whose parents were third cousins presented with intermittent claudication of the calves, thighs and buttocks along with chronic ischemic pain in their feet and joint pain in their hands. Plain x-rays revealed arterial calcification of the lower extremities (*N Engl J Med*. 2011;364:432-442).

Investigators used single-nucleotide-polymorphism to find a region in all 5 siblings for which the parents were heterozygous. From there, a mutation was identified in a gene that encodes *CD73*, an enzyme on the surface of vascular endothelial cells that converts adenosine monophosphate.

This discovery provided insights into other conditions that involve calcification of vessels including Fahr's syndrome, a calcification of vessels in the basal ganglia. The discovery also led to a protocol in which the family is being treated with bisphosphonates.

Unusual Cases

Successful cases such as this are unusual, Dr. Gahl said, adding that similar to Dr. Jacob's experience, the UDP only finds diagnoses in about a quarter of cases. The trick, he said, isn't simply finding candidate genes, but proving that the variant in that gene is causing the disease and identifying the mechanism of action to target an intervention.

"It doesn't happen often, but when it does, it can change the field because those are the new concepts," said Dr. Gahl.

"People's expectations about this are perhaps higher than they should be. People think if they can sequence their genes, they'll know all about their risks, but there's a lot of ambiguity."

Still, Dr. Gahl said, he expects the current 25% success rate to improve over the next few years. And the UDP keeps all patient samples so that if new patients with similar symptoms come in, analyzing the new cases can help inform the previous ones.

According to Dr. Jacob, the whole field of DNA sequencing is moving rapidly into the physician's office with its use in undiagnosed diseases and in oncology already realities.

"It's not a question of if this is going to be a part of medical practice; it's a question of when. As the price drops and the knowledge goes up and there's more and more evidence that this is useful for the practicing clinician, the faster this is going to happen."

Dr. Jacob and Dr. Gahl have reported no relevant financial relationships.

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