Cheaper, faster, more accurate test to identify gene defects in heart patients

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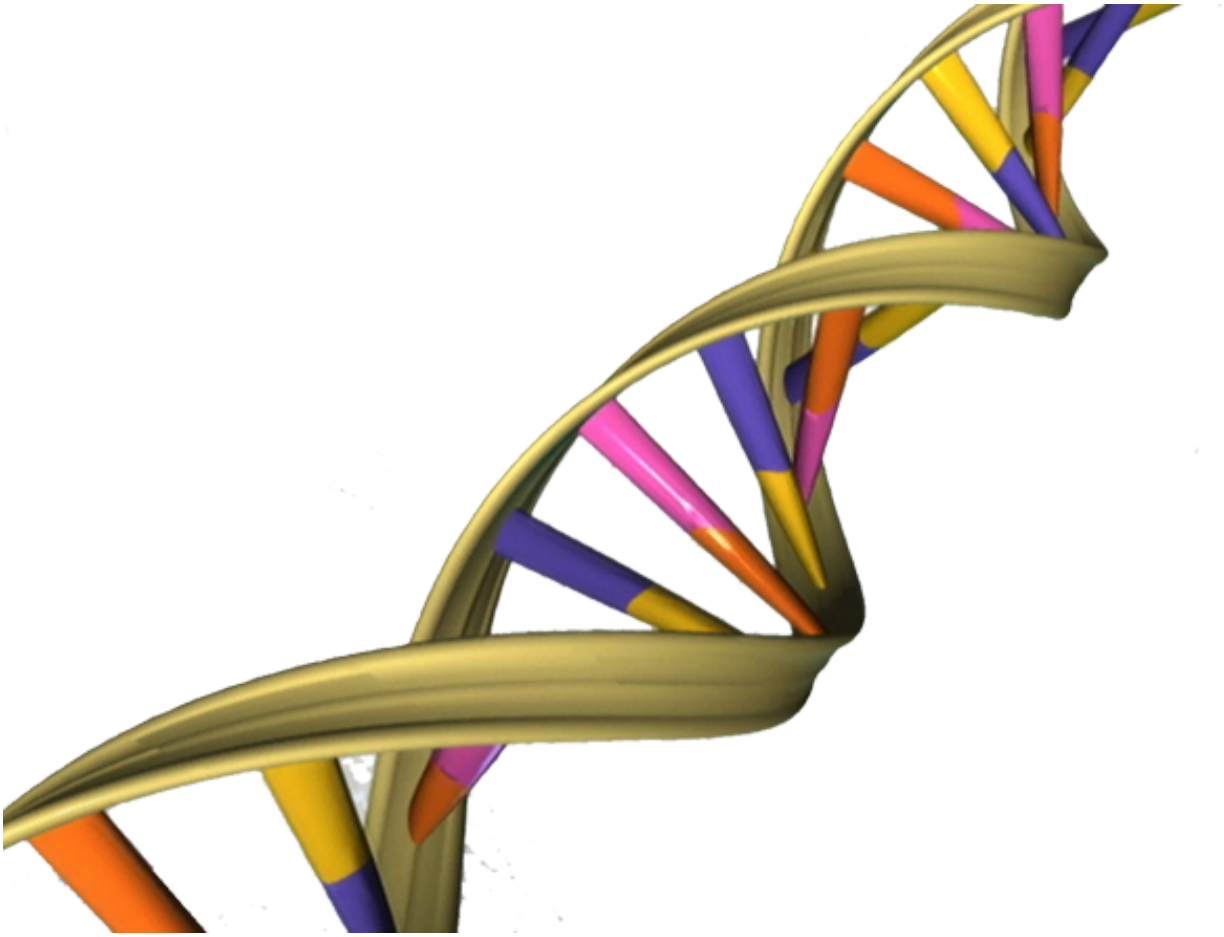

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

Stanford researchers design cheaper, faster, more accurate test to identify gene defects in heart patients

For the subset of heart patients whose illness isn't caused by a lifetime of cigarettes, trans fats or high glycemic foods, a new genetic test developed at the Stanford University School of Medicine may be able to accurately pinpoint the likely genetic causes of their conditions in just a couple of days.

In work that could advance precision health, Kitchener Wilson, MD, PhD, instructor of pathology, and Joseph Wu, MD, PhD, professor of cardiovascular medicine and of radiology, teamed up with a group of genome-sequencing specialists to develop the new technique: a better way to test cardiac patients for any genes that might be causing their problems.

Wilson and Wu said that the gold standard of genome sequencing involves thousands of genes, costs $1,000 or more and can take weeks or months to get results. For a patient with a heart condition that's difficult to diagnose, it makes no sense to sequence the entire 22,000-gene genome, since fewer than 200 genes are known to affect the heart, they said. Moreover, whole-genome sequencing typically contains mistakes, so key mutations might be missed.

To meet this challenge, Wilson and Wu's team designed a streamlined assay, or test, that looks at just the 88 genes known to carry mutations that cause heart problems. Materials for the new test cost about $100, and results are back within three days. Wilson and Wu are first and senior authors, respectively, on a paper describing the assay that will be published online Aug. 11 in *Circulation Research*.

This approach—surveying a small subgroup of relevant genes instead of the whole genome—is already used to test for other diseases, such as

cystic fibrosis. But cystic fibrosis involves only one gene, albeit with hundreds of variants. "By comparison, the heart diseases are more challenging just because there are so many genes to sequence," said Wilson. "To do that accurately has been difficult and, until now, too expensive for most labs."

Simple genetic probes

Such testing isn't for the typical, older cardiac patient who comes in with chest pain, the result of a lifetime of poor diet and little exercise. "Those patients can be treated with standard treatments, such as surgical interventions. But what if a 30-year-old woman comes in with chest pain and her doctors can't find any obvious reason why she should be having heart problems at such a young age?" said Wu, who is also the director of Stanford's Cardiovascular Institute. That could be the moment for doctors to break out the complementary long padlock probes for inherited heart disease.

Complementary long padlock probes, or cLPPs, were developed at the Stanford Genome Technology Center. These simple probes accurately target specific parts of the genome and can be made in large batches at low cost. Because of their simplicity, they are easily customized to target different genes. Wilson and Wu spearheaded the effort to put cLPPs to work diagnosing cardiac diseases.

A preliminary test of the assay on blood samples and some skin samples from 29 participants from families with inherited heart disease validated the cLPP approach, the researchers said. The heart disease cLPP assay was cheaper, faster and more accurate than whole-genome assays.

The Stanford team next plans to test the technique on a group of 200-300 patients. In the meantime, Wilson and Wu are offering the test free to any research lab that wants to try it. "They can just email me,"

said Wilson, "and we'll send them the assay, and then they can do it in their own lab—as long as they have some experience with next-generation sequencing."

The assay will shorten the time it takes to diagnose difficult or unusual heart disease cases, Wu said. "Suppose you have a 60-year-old patient who comes in with heart failure," he said. "We do the angiogram and we find he has no history of heart attack or other issues, and yet the heart is not performing well. We also find that several of his family members have similar heart conditions. So if we run the new genetic test and find the man's illness has a genetic cause, such as dilated cardiomyopathy, we now have both a cause and a diagnosis, and we can initiate treatment right away."

Avoiding a 'fishing expedition'

"Not having that result delays diagnosis and increases costs because you're going through a whole bunch of tests—sometimes it becomes a fishing expedition, which can be frustrating to both the physician and the patient," Wu added. "But perhaps the most important benefit is that you can give the patient accurate answers about his or her disease."

Wilson and Wu said the genome technology group has been working on the cLPP technique for a long time. "Our goal is to make genetic testing more accessible to more people," Wilson said. "We want to democratize it. For now, we're going to release it free of charge: Researchers can get samples of the assay so they can run it themselves. We're also releasing all of the technical data for the probes so researchers can recreate and modify the probes themselves. In some ways it's making genetic testing open source."

The development of the new test is an example of Stanford Medicine's focus on precision health, which aims to enable researchers and

physicians to better predict individual risks for specific diseases, develop approaches to early detection and prevention, and help clinicians make real-time decisions about the best way to care for patients.

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