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New method enables sequencing of fetal genomes using only maternal blood sample

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Researchers at the Stanford University School of Medicine have for the first time sequenced the genome of an unborn baby using only a blood sample from the mother.

The findings from the new approach, to be published July 4 in *Nature*, are related to research that was reported a month ago from the University of Washington. That research used a technique previously developed at Stanford to sequence a fetal genome using a blood sample from the mother, plus DNA samples from both the mother and father.

The whole genome sequencing in the new Stanford study, however, did not require DNA from the father — a significant advantage when a child's true paternity may not be known (a situation estimated to affect as many as one in 10 births in this country) or the father may be unavailable or unwilling to provide a sample. The technique brings fetal genetic testing one step closer to routine clinical use.

"We're interested in identifying conditions that can be treated before birth, or immediately after," said Stephen Quake, PhD, the Lee Otterson Professor in the School of Engineering and professor of bioengineering and of applied physics. "Without such diagnoses, newborns with treatable metabolic or immune system disorders suffer until their symptoms become noticeable and the causes determined." Quake is the senior author of the research. Former graduate student H. Christina Fan, PhD, now a senior scientist at ImmuMetrix, and current graduate student Wei Gu are co-first authors of the article.

As the cost of such technology continues to drop, it will become increasingly common to diagnose genetic diseases within the first trimester of pregnancy, the researchers believe. In fact, they showed that sequencing just the exome, the coding portion of the genome, can provide clinically relevant information.

In the new study, the researchers were able to use the whole-genome and exome sequences they obtained to determine that a fetus had DiGeorge syndrome, which is caused by a short deletion of chromosome 22. Although the exact symptoms and their severity can vary among affected individuals, it is associated with cardiac and neuromuscular problems, as well as cognitive impairment. Newborns with the condition can have significant feeding difficulties, heart defects and convulsions due to excessively low levels of calcium.

"The problem of distinguishing the mother's DNA from the fetus's DNA, especially in the setting where they share the same abnormality, has seriously challenged investigators working in prenatal diagnosis for many years," said Diana Bianchi, MD, executive director of the Mother Infant Research Institute at Tufts Medical Center, who was not involved in the Nature study. "In this paper, Quake's group elegantly shows how sequencing of the exome can show that a fetus has inherited DiGeorge syndrome from its mother." (Bianchi is chair of the clinical advisory board of Verinata Health Inc., a company that provides a fetal genetic test using earlier technology developed by Quake.)

Prenatal diagnosis is not new. For decades, women have undergone amniocentesis or chorionic villus sampling in an attempt to learn whether their fetus carries genetic abnormalities. These tests rely on obtaining cells or tissue from the fetus through a needle inserted in the uterus — a procedure that can itself lead to miscarriage in about one in 200 pregnancies. They also detect only a limited number of genetic conditions.

The new technique hinges on the fact that pregnant women have DNA from both their cells and the cells of their fetus circulating freely in their blood. In fact, the amount of circulating fetal DNA increases steadily during pregnancy, and late in the third trimester can be as high as 30 percent of the total.

In 2008, Quake's lab pioneered the use of the relative levels of fetal DNA in maternal blood to diagnose conditions caused by missing or extra chromosomes, such as Down syndrome. Four companies in the United States now market tests based on the technique to physicians and parents, and demand for the service is increasing steadily. (Quake's specific approach was licensed by Stanford to Redwood City-based Verinata and South San Francisco-based Fluidigm Inc. Neither company was involved in the current study.) These tests, however, do not provide a full-genome profile, and cannot identify more-subtle genetic anomalies that occur within chromosomes and other DNA.

This study takes the blood-sampling test one step farther by recognizing that circulating fetal DNA contains genetic material from both the mother and the father. By comparing the relative levels in the mother's blood of regions of maternal (from both the mother and the fetus) and paternal (from the fetus only) DNA known as haplotypes, the researchers were able to identify fetal DNA from the mix and isolate it for sequencing. The method differs from that of the University of Washington group by inferring the father's genetic contribution, rather than sampling it directly (through saliva).

The Stanford team tried its method in two pregnancies. One of the mothers had DiGeorge syndrome; the other did not. Their whole genome and exome sequencing showed that the child of the woman with DiGeorge syndrome would also have the disorder. The finding was confirmed by comparing the predicted fetal genome sequence with the sequence obtained immediately after birth from umbilical cord blood.

Although the experiments were performed retrospectively and these women and their babies remained anonymous, a similar finding in a real clinical setting would likely prompt doctors to assess the baby's heart health and calcium levels shortly after birth.

"Three years ago we were very excited about successfully validating non-invasive fetal aneuploidy detection," said study co-author Yair Blumenfeld, MD, a clinical assistant professor of obstetrics and gynecology at Stanford medical school. "But we always knew that detecting fetal chromosomal abnormalities was just the tip of the iceberg, and that diagnosing individual gene defects was the future. This important study confirms our ability to detect individual fetal gene defects simply by testing mom's blood."

The researchers plan to continue to develop the technology for eventual use in the clinic.

In addition to Quake, Gu, Fan and Blumenfeld, other Stanford scientists involved in the research include graduate student Jianbin Wang and professor of obstetrics and gynecology Yasser El-Sayed, MD.

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