New method of selecting DNA for resequencing accelerates discovery of subtle DNA variations

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A new technology developed by scientists at Emory University will allow researchers to more easily discover subtle and overlooked genetic variations that may have serious consequences for health and disease. Called Microarray-based Genomic Selection (MGS), the research protocol allows scientists to extract and enrich specific large-sized DNA regions, then compare genetic variation among individuals using DNA resequencing methods.

The technology reported will be published online on Oct. 14 and will appear in the November print issue of the journal *Nature Methods*.

Lead author is David Okou, PhD, postdoctoral fellow in the laboratory of Michael Zwick, PhD, assistant professor of human genetics at Emory University School of Medicine.

The goal of most human genetics researchers is to find variations in the genome that contribute to disease. Despite the success of the human genome project and the availability of a number of next-generation DNA sequencing platforms, however, the lack of a simple, inexpensive method of selecting specific regions to resequence has been a serious barrier to detecting subtle genetic variability among individuals. The Emory scientists believe that goal will be much more obtainable thanks to MGS.

MGS uses DNA oligonucleotides (probes) arrayed on a chip at high density (microarray) to directly capture and extract the target region(s) from the genome. The probes are chosen from the reference human genome and are complementary to the target(s) to capture. Once the target is selected, resequencing arrays or other sequencing technologies can be used to identify variations. The Emory scientists believe MGS will allow them to easily compare genetic variation among a number of individuals and relate that variation to health and disease.

"The human genome project focused on sequencing just one human genome--an amazing technological feat that required a very large industrial infrastructure, hundreds of people and a great deal of money," says Dr. Zwick. "The question since then has been, can we replicate the ability to resequence parts of the genome, or ultimately the entire genome, in a laboratory with a single investigator and a small staff? The answer is now 'yes.'"

Geneticists have found many different types of obvious gene mutations that are deleterious to health, explains Dr. Zwick, but more subtle variations, or variations located in parts of the genome where scientists rarely look, may also have negative consequences but are not so easily discovered.

Other methods for isolating and studying a particular region of the genome, such as PCR and BAC cloning (bacterial artificial chromosomes) are comparatively labor intensive, difficult for single laboratories to scale to large sections of the genome, and relatively expensive, says Dr. Zwick.

Whereas typical microarray technology measures gene expression, MGS is a novel use of microarrays for capturing specific genomic sequences. For the published study, a third type of microarray--a resequencing array--was used to determine the DNA sequence in the patient samples.

"The logic behind the resequencing chip is that you design the chip to have the identity of the base at every single site in a reference sequence," says Dr. Zwick. "You use the human genome reference sequence as a shell and you search for variation on the theme. This alternative new technology allows a regular-sized laboratory and single investigator to generate a great deal of data at a cost significantly less than what a sequencing center would charge," Dr. Zwick says.

Source: Emory University