MedicalXpress

Next generation sequencing shakes up genotype/phenotype correlation, disease discoveries

August 13 2014

With the ability to use next generation sequencing technology, researchers have a broadened understanding of the association of genetic changes and disease causation to a much greater resolution, driving new discoveries, said clinical geneticists from Baylor College of Medicine in Houston and the University of Montreal in Canada in a perspective published today in the *New England Journal of Medicine*.

Authors Dr. Brendan Lee and James T. Lu of Baylor, and Dr. Phillippe Campeau of the University of Montreal, discuss the impact on the increased use of these technologies—such as whole genome and whole exome sequencing which give insight into a person's complete DNA (whole genome) and all protein coding genes (exome) – on the expanding collection of diseases with different genetic lesions.

Now it's the genotype—not as much the phenotype—that drives detection of the disease, the authors noted.

"Up until about the last five years, we have had relatively crude tools to interpret whether a mutation causes a disease," said Lee, professor and interim chair of molecular and human genetics at Baylor. "Typically we could only conclude that a genetic mutation was disease causing when it caused a dramatic alteration in the protein"

As the cost of next generation sequencing continues to drop, and is used

more often, scientists are observing at much greater resolution and sensitivity how subtle gene changes may be associated with unique disease presentations, even in previously undiagnosed forms of disease.

"We are observing increasing complexity in the association of disease and genes. There are many different types of mutations in many different genes that can cause a specific disease grouping or even quite different disease groups – more than we ever thought," said Lee. "Twenty years ago, we could only identify disease genes based on finding severe mutations in a recognized group of clinical features. Now we find often unique mutations in many different genes causing either similar or different disease conditions."

Use brittle bone disease for example, Lee said.

"We used to think that if you have frequent bone fractures and loose connective tissue, you have brittle bone disease caused by genetic lesions in type I collagen," he said. "Now we know that mutations in more than 13 genes can contribute to the cause of brittle bone disease. There can be really rare patients with a mutation in a very specific gene which alters its function in a unique way- not simply loss or gain of the normal function of this gene."

Lee added much of this has been driven by discoveries at Baylor's Department of Molecular and Human Genetics (the number one National Institutes of Health funded genetics program in the country) in collaboration with Baylor's Medical Genetics Laboratories and Human Genome Sequencing Center.

Next generation sequencing has taught scientists about new associations of functions of genes not appreciated before, Lee, also an investigator of the Howard Hughes Medical Institute, said. "The genetic revolution has had a huge impact on the way we study human disease and reaches every

specialty in medicine."

Provided by Baylor College of Medicine