Use of “Long Read” Gene Sequencing Allows University of Washington Researchers to Uncover Thousands of Never-before Seen Gene Variations

Category: Digital Pathology (http://www.darkdaily.com/category/laboratory-pathology/digital-pathology-laboratory-pathology-2), Instruments & Equipment (http://www.darkdaily.com/category/laboratory-pathology/instruments-equipment), Laboratory Instruments & Laboratory Equipment (http://www.darkdaily.com/category/laboratory-pathology/laboratory-instruments-laboratory-equipment), Laboratory News (http://www.darkdaily.com/category/laboratory-pathology/laboratory-news), Laboratory Operations (http://www.darkdaily.com/category/laboratory-pathology/laboratory-operations), Laboratory Pathology (http://www.darkdaily.com/category/laboratory-pathology)

Published: June 24 2015

This and similar research initiatives expected to increase the number of genetic markers that would be useful for creating clinical pathology laboratory tests and therapeutic drugs

Whole human genome sequencing continues to become faster, easier, cheaper, and more accurate to do. Because of these advances, the sheer number of human genomes being sequenced is skyrocketing. This huge increase in data is helping researchers unlock many new insights that, in turn, are fueling efforts to develop useful new medical laboratory (https://en.wikipedia.org/wiki/Medical_laboratory) tests and therapeutic drugs.

This is happening at the University of Washington (http://www.washington.edu/) (UW), where researchers using new genome sequencing technology are uncovering thousands of never-before-seen genetic variants. The application of “long read” gene sequencing technologies is allowing these researchers to identify genetic variants previously unknown, and that are made up of between 50 and 5,000 base pairs.

The discovery is important for two reasons. First, it could close existing gaps in the genome map. Second, it could help scientists identify new genomic variations that are closely associated with difficult-to-diagnose diseases. Of interest to pathologists (https://en.wikipedia.org/wiki/Pathology) and clinical laboratory (https://en.wikipedia.org/wiki/Medical_laboratory) professionals, such discoveries could point to expanded use of genetic testing for diagnosis and treatment of disease.

New Sequencing Technology Could Close Remaining Gaps in Genome

In 2009, *Dark Daily* (http://www.darkdaily.com) published an e-briefing (http://www.darkdaily.com/two-biotech-firms-pull-ahead-in-race-for-1000-human-genome-sequence) to update readers on a new genome sequencing (https://en.wikipedia.org/wiki/Whole_genome_sequencing) technology called SMRT (http://en.wikipedia.org/wiki/Single_molecule_real_time_sequencing (single-molecule, real-time)), developed by Pacific Biosciences Inc. (http://www.pacificbiosciences.com) of Menlo Park, California. It was this technology the UW team used to sequence a hydatidiform mole (H mole) (http://en.wikipedia.org/wiki/Molar_pregnancy) genome for the study. They used this particular genome in order to simplify the process of searching for variants,

explained a ***Medical Xpress*** **article (http://medicalxpress.com/news/2014-11-thousands-never-before-seen-human-genome-variations.html)** .

An H mole is a rare, abnormal growth that forms inside the uterus. It occurs when a sperm fertilizes an egg that lacks the DNA from the mother. As a result, the H mole genome contains only one copy of each gene, instead of the two copies of a normal cell. This single-copy genome made it easier for the UW researchers to search for genetic variations.

"We now have access to a whole new realm of genetic variation that was opaque to us before," stated team leader, **Evan Eichler, Ph.D. (https://eichlerlab.gs.washington.edu/evan.html)** , in the *Medical Xpress* story. Dr. Eichler is Professor of Genome Sciences at UW. He and his team were able to identify and sequence 26,079 segments in the H mole that were different from a standard human reference genome. Around 22,000 of these had never been reported before.

The researchers reported their findings in the **Nov. 10 issue of the journal *Nature* (http://www.nature.com/nature/journal/v517/n7536/abs/nature13907.html)** .

(http://www.darkdaily.com/wp-content/uploads/Evan-Eichler-Ph.D.jpg)

Evan Eichler, Ph.D., Professor of Genome Sciences at UW, and his colleagues, have uncovered thousands of never-before-seen genetic variants. They are exploring the use of new technologies that could help close existing gaps in the mapping of the human genome. (Photo copyright Clare McLean/*Medical Xpress.*)

Conventional Genomic Sequencing Misses Many Important Structural Variations

Using conventional "short-read" sequencing methods, scientists have remained unable to accurately identify about half of the genetic causes of inherited conditions, the *Medical Xpress* writer noted. They are still unable to precisely map many parts of the genome. "The human genome is considered sequenced, yet more than **160 euchromatic (http://en.wikipedia.org/wiki/Euchromatin)** gaps remain, and many aspects of its structural variation are poorly understood," observed Eichler in the Nature article.

This "**missing heritability problem (http://en.wikipedia.org/wiki/Missing_heritability_problem)** " has significant implications for medicine. The reason: susceptibility to disease may depend more on "the combined effect of all the genes in the background than on the disease genes in the foreground," a ***Technology Review*** **story (http://www.technologyreview.com/featuredstory/422142/the-genomes-dark-matter/)** on the genome's dark matter reported. Some observers believe that part of the missing heritability problem could be due to the limitations of conventional genome sequencing technologies.

"Long-read" Sequencing Technology Gives Researchers New Tool for Analysis

Standard sequencing technologies map genomes by aligning hundreds of millions of small, overlapping segments of DNA. These are usually made up of about 100 base pairs. Researchers then analyze the DNA sequences to construct a map of the genome, *Medical Xpress* reported.

This conventional method has allowed scientists to identify very small variations in the genome and very large variations. The small variations include single nucleotide polymorphisms (SNP). The large variations involve segments of DNA 5,000 bases in length or longer. However, the *Medical Xpress* reporter wrote, reliably detecting variations in DNA segments ranging from about 50 to 5,000 base pairs in length has remained a challenge due to technical limitations.

The new SMRT sequencing technology can reveal variant types that have been inaccessible with conventional sequencing. These include **single nucleotide variants (http://en.wikipedia.org/wiki/Single_nucleotide_polymorphism)** , large insertions, deletions, inversions, translocations, and repeat expansions.

Link Between Genetic Variation and Important Phenotypes

The new "long-read" sequencing capability could allow scientists to develop a genomic structural variation map with a much higher resolution than was previously possible. In **an article on its website (http://www.pacificbiosciences.com/applications/human/)** , Pacific Biosciences suggested that this is significant because it could expand understanding of how sequence variation is linked to important expressed physical traits.

Important for healthcare professionals, including pathologists and clinical laboratory scientists, this could eventually open the way for new therapeutics and associated medical laboratory tests for the diagnosis and treatment of disease.

—Pamela Scherer McLeod

Related Information:

Resolving the Complexity of the Human Genome Using Single-molecule Sequencing (http://www.nature.com/nature/journal/v517/n7536/abs/nature13907.html)

The Genome's Dark Matter (http://www.technologyreview.com/featuredstory/422142/the-genomes-dark-matter/)

Two Biotech Firms Pull Ahead in Race for $1,000 Human Genome Sequence (http://www.darkdaily.com/two-biotech-firms-pull-ahead-in-race-for-1000-human-genome-sequence)

Leave a Reply

Name (required)