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Redefining Single-Cell Whole Exome Sequencing

New C1™ System Application Could Transform the Discovery of Causal Disease Mutations

SOUTH SAN FRANCISCO, Calif., Oct.2, 2014 -- Clinical researchers race against an invisible clock to discover mutations responsible for complex diseases such as cancer, Alzheimer's, and autoimmune disorders that afflict their patients. They often use bulk exome sequencing to identify the genetic changes that trigger the disease's onset; however, the mutations found to date do not adequately explain the origin or reoccurrence of disease. Fluidigm's newest application, Single-Cell Whole Exome Sequencing workflow for its C1™ Single-Cell Auto Prep System, is designed to help researchers accelerate the discovery of novel functional variants that may alter protein function.

The exome represents an important part of the genome. While the exome encompasses less than 2% of the 3.2 billion bases found in the human genome, it is responsible for encoding most proteins. Over 85% of known disease-associated genetic traits are located in the exome. Because mutations in the exome can be easily translated for clinical application, exome sequencing is a critical tool for discovery-driven research.

"The commercialization of single-cell whole exome sequencing on the C1 is perhaps the most significant contribution Fluidigm has made since we pioneered single-cell gene expression. Analyzing the exomes of single cells allows a level of understanding that is unattainable with bulk sequencing. Specifically, researchers can now determine precisely which cells contain which mutations or variations; whether mutations segregate into specific sub-populations, or are distributed more stochastically; and if mutations tend to concentrate in highly variant cells. This is a level of understanding that is uniquely enabled by the single cell-whole exome workflow," said Gajus Worthington, Fluidigm President and Chief Executive Officer.

"We would like to build personalized panels (genetic tests) for particular tumors in order to identify mutations and understand the implications in both inherited and sporadic cancers," says Dr. Ioannis Ragoussis, Head of Genomic Sciences at McGill University. "Currently, we can demonstrate that breast cancer tumors are physiologically diverse but understanding the clonal evolution and how mutations accumulate is difficult in bulk samples."

Dr. Ragoussis is finding that rare and acquired mutations are difficult to detect with current bulk-sampling methods in which thousands of cells are sequenced together. With a sequencing error rate of 1-3%, bulk sequencing can obscure less abundant cell populations and the rare variants they harbor. Single-cell exome sequencing provides a new level of sensitivity to help find rare, novel mutations across all protein coding regions of the genome.
Using Fluidigm's new workflow, the C1 system can help researchers conduct single-cell exome sequencing experiments faster and far more efficiently. The methodology speeds up the overall process by 3X and reduces the total cell and library preparation time to less than 24 hours. The protocol also drops the cost of sample preparation for single-cell whole exome sequencing from a high of $600 per cell down to approximately $26 per cell.

Discovering the Root of Cancer

One of the areas in which Fluidigm's Single-Cell Whole Exome Sequencing protocol is being implemented is the study of the genetic origins of cancer. The U.S. National Institute of Health (NIH) has funding of more than $100 million designated to support more than 150 projects using Cancer Exome Sequencing.
Single-cell whole exome sequencing can help researchers discover diagnostic and prognostic biomarkers, identifying predictive variants known to affect critical pathways and disrupt normal states. Identifying such risk markers can give new insight into a given person's susceptibility to primary and secondary disease. Single-cell whole exome sequencing can also help identify mutation profiles to guide therapeutic treatment decisions and predict drug response.

Technology

The Fluidigm C1 Single-Cell Auto Prep System is based on the company's innovative microfluidic technology that enables researchers to rapidly and reliably isolate, process, and profile individual cells for genomic analysis. The Single-Cell Whole Exome Sequencing workflow is the fifth application enabled on the C1 system, which currently supports targeted gene expression, mRNA sequencing, miRNA expression profiling, and targeted DNA sequencing.

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