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Researchers Uncover Low-Frequency Hepatitis B Drug-Resistant Mutations Using 454 Sequencing Systems.

Study results show improved sensitivity for detecting low-prevalence resistance variants when compared to traditional methods.

A study published online last week in the Journal of Infectious Disease reports that ultra-deep sequencing has the ability to identify low-frequency hepatitis B virus (HBV) drug-resistant mutations in infected samples, including mutations undetected by standard direct PCR sequencing methods (1). The paper outlines the results of a collaborative study between Stanford University and 454 Life Sciences, a Roche Company, that used 454 Sequencing systems to examine blood samples from nucleoside and nucleotide reverse-transcriptase inhibitor (NRTI) treated and untreated individuals. The study provides new insights into the dynamics of early stage NRTI resistance in HBV as current methods limit detection to mutations only after they have become prevalent.

Hepatitis B virus is a chronic disease which causes severe inflammation of the liver. Similar to HIV, HBV reverse-transcriptase has a high rate of replication which generates an ever increasing quantity of potentially drug-resistant strains within a host. Current methods for characterizing HBV sequence variability, such as direct PCR sequencing or “population based” sequencing detect mutations present to only >20% of the virus population. By using unbiased, highly sensitive ultra-deep sequencing, the researchers at Stanford University, led by Dr. Robert Shafer and Dr. Severine Margeridon-Thermet, were able to detect a variety of drug-resistant mutations present in as little as 1% of the population. In fact, the study found HBV drug-resistant mutations in 10 samples from 5 NRTI-treated individuals that were not detected by PCR. Additionally, several samples were found by ultra-deep sequencing to be co-infected with both A and G genotypes when direct PCR sequencing had only detected genotype G.

“This study demonstrates the power of ultra-deep sequencing to uncover previously obscured HBV drug resistance,” said Dr. Robert Shafer, principal author and Associate Professor of Infectious

Disease at Stanford University. “The expanded perspective on emerging and latent HBV drug resistance, provided by this method, may make it possible to improve the strategic use of HBV drugs to treat this lifelong infection in the future.”

“This paper complements our work with detection of low-frequency mutations in HIV by providing similar insights into another chronic viral infection, hepatitis B virus ” explained Michael Egholm, co-author and Chief Technology Officer at 454 Life Sciences. “We are excited to see the technology applied to these types of real-world problems and we are confident that it will change the way infectious diseases are monitored and treated in the future.”

454 Life Sciences, a center of excellence of Roche Applied Science, develops and commercializes the innovative 454 Sequencing System for ultra-high-throughput DNA sequencing. Specific applications include de novo sequencing and re-sequencing of genomes, metagenomics, RNA analysis, and targeted sequencing of DNA regions of interest. The hallmarks of the 454 Sequencing System are its simple, unbiased sample preparation and long, highly accurate sequence reads, including paired-end reads. The technology of the 454 Sequencing System has enabled hundreds of peer-reviewed studies in diverse research fields, such as cancer and infectious disease research, drug discovery, marine biology, anthropology, paleontology and many more.

About Roche

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(1) Margeridon-Thermet et al. Ultra-Deep Pyrosequencing of Hepatitis B Virus Quasispecies from Nucleoside and Nucleotide Reverse-Transcriptase Inhibitor (NRTI)-Treated Patients and NRTI-Naïve patients. (2009) Journal of Infectious Disease. ePub March 16.

For further information please contact:

Roche Diagnostics

Dr. Burkhard Ziebolz

Phone: +49 8856 604830

Email: burkhard.ziebolz@roche.com

454 Life Sciences Corporation, a Roche company

Dr. Ulrich Schwoerer

Phone: 203-871-2300

Email: ulrich.schwoerer@roche.com