Team builds modeling systems identifying gene-drug and environment interaction

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A team of researchers at the Icahn School of Medicine at Mount Sinai and the University of Washington has designed a modeling system that integrates genomic and temporal information to infer causal relationships between genes, drugs, and their environment, allowing for a more accurate prediction of their interactions over time. The work is described in a paper published today in *Nature Communications*.

"Understanding how a person's environment, diet, medications, and other factors impact disease-associated traits over time has the potential to more accurately model an individual's risk of disease," says Eric Schadt, Ph.D., Dean for Precision Medicine at the Icahn School of Medicine at Mount Sinai; CEO of Sema4, a Mount Sinai venture; and a co-author of the paper. "This will be the future of precision health or personalized medicine."

Given the complexity of biological systems, scientists at the Icahn School of Medicine believed that it would only be possible to increase the accuracy of prediction tools by examining gene expression and other data in response to various perturbations at multiple points over time. The tools they created measure both static and dynamic changes in order to identify the web of causal relationships among molecular elements that make up regulatory networks.

"Predicting the behavior of biological systems is tremendously difficult because they are so dynamic, adapting as conditions demand. It is only by mining as much data as possible that we can generate more reliable results about how anyone's health might change as a result of exposure to certain environmental or other elements," said Jun Zhu, Ph.D., Professor of Genetics and Genomic Sciences at the Icahn School of Medicine, Head of Data Sciences at Sema4, and senior author of the publication. "Our new tools offer a fundamental step forward by analyzing genomic data over time. This type of approach will be particularly useful for medical research on aging and ultimately could enhance our ability to predict disease risk, making earlier interventions possible to treat or prevent disease altogether. "

The scientists evaluated their tools by analyzing a genetically heterogenous population of yeast cells treated with rapamycin, a potential anti-aging drug, profiling the population at multiple time points. The results demonstrated that the new approach identified a

significant amount of associations between DNA variation and gene expression variation, especially for aging-related genes, reflecting the changing impact of genetic variations over time. Further, this approach proved more reliable in identifying causal regulators of gene-drug interactions, compared to conventional methods using only a single time point.

"This paper demonstrates the improvements in inferring genetic causes of disease enabled by higher-resolution molecular profiling. As scientists become increasingly able to incorporate information such as temporal, single-cell, and microenvironment profiling into studies, algorithms such as the one described in Dr. Lin's paper will be poised to leverage such data to infer increasingly accurate models of the molecular drivers of disease which can be used to design improved novel therapies." said Adam Margolin, Ph.D., Chair of the Department of Genetics and Genomic Sciences and Senior Associate Dean for Precision Medicine at the Icahn School of Medicine.

More information: Luan Lin et al, Temporal genetic association and temporal genetic causality methods for dissecting complex networks, *Nature Communications* (2018). DOI: 10.1038/s41467-018-06203-3

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