Cardiovascular Genetics: A News Round-Up

Omics Gets Personal
Integrative Profiling of Health and Disease

Jane F. Ferguson, PhD


Study Hypothesis
Increasing accessibility to genomic and phenotypic information through the use of high-throughput techniques is greatly advancing the possibility of personalized medicine as a tool to both treat and prevent disease. However, interpreting genomic data to effectively predict disease risk in healthy individuals remains particularly challenging. Cohesive, wide-ranging approaches are required to integrate multiple levels of omics data (eg, genomic, transcriptomic, proteomic, metabolomic) with physiological data during healthy and disease states. In this study, the authors hypothesized that extensive profiling of an individual at multiple times, encompassing multiple physiological conditions, would allow for increased understanding of dynamic health and disease states, improving the ability to predict and treat disease.

How Was the Hypothesis Tested?
Blood samples were obtained from a healthy 54-year-old man over a 14-month study period, with additional available laboratory analyses extending the total observation time to 24 months. Extremely deep, whole-genome sequencing was conducted using 2 different platforms, whereas exome sequencing was carried out using 3 different platforms. This multiplatform approach allowed for high-confidence calling of variants and identification of novel and unannotated genetic regions. In addition, whole-genome sequencing of the subject’s mother facilitated phasing and completion of a high-quality individual genome. High-coverage whole-transcriptome sequences were obtained at 20 different time points. Concurrently, proteomic profiling of peripheral blood mononuclear cells and serum, in addition to serum metabolomics, allowed for detailed analysis of physiological changes over the 14-month period. Autoantibody profiling as well as clinical and biochemical analyses were carried out in complement. Two incidences of viral infection allowed for monitoring of both healthy and disease states as well as of response to lifestyle interventions. A bioinformatic pipeline using a Fourier spectral analysis approach to normalize data sets was used to integrate the multiple layers of data over the study period. Numerous publically available analysis tools were used for clustering and enrichment analysis to detect signatures of dynamic changes over time and during disease states. These data were compiled and analyzed to produce an integrative personal omics profile.

Principal Findings
High-coverage whole-genome and transcriptome sequencing allowed for identification of rare or private mutations, alternative splicing, heteroallelic expression, RNA editing, and miRNA expression. Based on genotype at established disease loci, the subject was predicted to be at increased risk for hypertriglycerideremia and type 2 diabetes as well as for basal cell carcinoma. Measurement of plasma triglycerides confirmed elevated levels, which subsequently were successfully reduced with simvastatin treatment. In addition, both the subject and his mother shared a mutation in the telomerase reverse transcriptase gene TERT that was previously associated with aplastic anemia. However, neither exhibited symptoms of aplastic anemia, and telomere length was determined to be normal. The subject contracted 2 infections during the course of the study: a human rhinovirus on day 0 and a respiratory syncytial virus (RSV) on day 289. An increase in multiple cytokines and C-reactive protein level was observed in response to both infections. In addition, autoantibody profiling revealed multiple antigens with increased reactivity during the human rhinovirus infection, including docking protein 6, an insulin receptor binding protein. Transcriptomic analysis revealed both upregulated and downregulated sets of genes in response to infection, containing significant enrichment for certain pathways, including protein metabolism and influenza life cycle (upregulated), and T-cell receptor signaling, B-cell signaling, lysosome, androgen regulation, and insulin signaling and response (downregulated). In addition, there was a spike in expression of major histocompatibility genes following the RSV infection. Combination of transcriptomic, proteomic, and metabolomic profiles revealed common signatures of response to RSV infection, including enrichment of phagosome, lysosome, protein processing, and

From the Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA.
Correspondence to Jane F. Ferguson, PhD, Perelman School of Medicine, University of Pennsylvania, 11-170 Translational Research Center, 3400 Civic Center Blvd, Bldg 421, Philadelphia, PA 19104. E-mail jfer@mail.med.upenn.edu
(Circ Cardiovasc Genet. 2012;5:381-382.)
© 2012 American Heart Association, Inc.
Circ Cardiovasc Genet is available at http://circgenetics.ahajournals.org
DOI: 10.1161/CIRCGENETICS.112.963801

381

Downloaded from http://circgenetics.ahajournals.org by guest on July 6, 2017
insulin pathways. Remarkably, despite normal glucose levels at baseline and throughout the first part of the study, the subject was given a diagnosis of type 2 diabetes ~1 year after study initiation. The subject was a nonsmoker and maintained a normal body weight throughout. The increase in glucose levels coincided with the RSV infection, with glucose elevation first occurring 12 days after infection and continuing for several months thereafter. Hemoglobin A1c was also found to be increased in the subject during this time. Interestingly, there was a spike in cytokines at day 12 of the RSV infection. Therapeutic interventions, including dietary changes, increased exercise, and low-dose acetylsalicylic acid, resulted in a return to normal glucose levels after several months.

**Implications**

These analyses demonstrate the utility of integrating multiple longitudinal samples and reveal acute changes in physiological states that would not be observed at a single time point or from a single analysis method. By eliminating interindividual variation, the analysis of one individual may allow for discovery of novel patterns, such as the potential relationship observed between RSV infection and diabetes. Although genomic information can be used to predict disease risk, these predictions may become much more informative with the addition of broader physiological profiling. By identifying omic signatures of varying health and disease states and in response to pharmacological or lifestyle interventions, we may improve our understanding and ability to monitor, predict, and treat on a personalized level.

**Acknowledgments**

The author is a member of the Early Career Committee of the American Heart Association Functional Genomics and Translational Biology Council.

**Disclosures**

None.
Omics Gets Personal: Integrative Profiling of Health and Disease
Jane F. Ferguson

doi: 10.1161/CIRCGENETICS.112.963801
Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2012 American Heart Association, Inc. All rights reserved.
Print ISSN: 1942-325X. Online ISSN: 1942-3268

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circgenetics.ahajournals.org/content/5/3/381

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Genetics can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Genetics is online at:
http://circgenetics.ahajournals.org//subscriptions/