Cardiovascular Genetics: A News Round-Up

Expression Quantitative Trait Locus Analysis Identifies Novel Genes for Statin Myopathy

Deepak Voora, MD

Principal Findings

In their gene expression and genetic data set of lymphoblastoid cell lines, 4590 genes with cis-eQTLs (defined as eQTLs within 1 MB of the transcription start/end site) were identified, and the expression of 5509 genes changed in response to simvastatin exposure. However, when the authors combined these analyses to identify transcripts that changed differently depending on genotype, they narrowed these large lists to only 6 loci that met criteria for a genome-wide significance level.

The top loci included a large group of variants near the GATM gene, and carriers of the minor allele had a decrease in GATM expression in response to simvastatin. Because of the known role of GATM in muscle physiology, the authors then hypothesized that these same variants may underlie the risk for statin-induced myopathy. Using data from 2 previous cohorts of cases of statin-induced myopathy, the authors confirmed that the same loci near GATM were protective for statin-induced myopathy in these patient cohorts.

How Was the Hypothesis Tested?

To test their hypothesis, the authors took advantage of a unique resource in pharmacogenomics research. From a prior study (Cholesterol and Pharmacogenetics [CAP] Study) in which volunteers were exposed to 6 weeks of 40 mg/d simvastatin, the authors banked 480 lymphoblastoid cell lines from study participants. This resource allowed the authors to expose lymphoblastoid cell lines to simvastatin in vitro to assess drug-induced changes in genome-wide gene expression. To carry out this work, banked lymphoblastic cell lines with genome-wide genotype data from 480 individuals were exposed to simvastatin in vitro, and gene expression was measured before and after drug exposure. Lymphoblastic cell lines have been available for a variety of studies focused on the genetic determinants of gene expression (ie, expression quantitative trait loci [eQTLs]) or changes in gene expression in response to in vitro exposure to medications. Mangravite et al1 combine these 2 concepts together to identify differential eQTLs or genetic loci that exert an influence on the magnitude or direction of gene expression changes in response to drug exposure. The underlying assumption is that genetically determined variation in drug responses can be revealed by differential changes in gene expression between those with different genotypes. Based on the known biology surrounding their top hit, the authors then tested for associations of their variants of interest with clinical responses to simvastatin therapy from 2 independent patient cohorts.

Study Hypothesis

Inhibitors of 3-hydroxy-3-methylglutaryl-CoA reductase (or statins) are the most common and effective medications used for the treatment and prevention of cardiovascular morbidity and mortality. Statins exert their beneficial effects primarily by inhibiting hepatic cholesterol synthesis. In general, statins are well-tolerated medications. However, a small but clinically significant number of patients taking statins develop statin myopathy, a range of clinical syndromes characterized by common muscle aches and pains to a rare but sometimes fatal condition of frank muscle necrosis called rhabdomyolysis. Although often described as benign, statin-induced side effects can significantly affect quality of life and are a frequent cause of premature drug discontinuation. As a consequence, millions do not receive the cardiovascular benefits of these life-saving drugs.

The reasons that some patients do (or do not) develop statin-induced side effects have been difficult to identify. Certain patient characteristics such as age, sex, and concomitant medications have been implicated in some. Genome-wide association studies have implicated specific genetic variants in the SLCO1B1 gene that underlie statin-induced side effects. However, many people without these genetic variants still go on to develop side effects, and many people who develop side effects have normal genotypes. Therefore, there are large gaps in our understanding surrounding not only the biology of statin-induced side effects but also useful biomarkers to identify individuals at highest risk for side effects. To overcome these gaps, Mangravite et al3 take an innovative approach to make a significant advancement in this field. The authors tested the hypothesis that genetic determinants of the gene expression response to in vitro simvastatin also underlie variability in the clinical response to this commonly used medication.

Expression Quantitative Trait Locus Analysis Identifies Novel Genes for Statin Myopathy

Deepak Voora, MD


From the Division of Cardiology, Genomic Medicine, Institute for Genome Science & Policy, Duke University, Durham, NC.

Correspondence to Deepak Voora, MD, Division of Cardiology, Genomic Medicine, Institute for Genome Science & Policy, Duke University, 905 S Lasalle Dr DUMC 3445, Durham, NC 27705. E-mail deepak.voora@duke.edu

(Circ Cardiovasc Genet. 2014;7:220–221.)

© 2014 American Heart Association, Inc.

Circ Cardiovasc Genet is available at http://circgenetics.ahajournals.org

DOI: 10.1161/CIRCGENETICS.114.000611
Implications
The mechanisms by which statin induced reductions in GATM may alter the risk of statin-induced myopathy are not clear from this study. However, this work opens the possibility of using the differential eQTL approach in lymphoblastic cell lines as a general platform to understand the variability in drug responses. Beyond statins, one can envision testing entire panels of medications using banked cell lines to identify novel mechanisms that underlie variable drug responses or to compare drugs with different mechanisms for their effects on gene expression in different genetic backgrounds. By demonstrating the feasibility of this approach, this work should dramatically accelerate our understanding of the response to medications used to treat cardiovascular disease.

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

Disclosures
None.

Key Words: gene expression regulation ■ genome-wide association study ■ genomics ■ pharmacogenetics
Expression Quantitative Trait Locus Analysis Identifies Novel Genes for Statin Myopathy
Deepak Voora

doi: 10.1161/CIRCGENETICS.114.000611
Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 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/7/2/220

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/