Variation in the ATM Gene May Alter Glycemic Response to Metformin

Nicole L. Glazer, PhD

The WTCCC2 (Wellcome Trust Case Control Consortium 2) study conducted a genome-wide association study of metformin response in individuals with type 2 diabetes, using the GoDARTS (Genetics of Diabetes Audit and Research Tayside Study) cohort, a large Scottish cohort of European ancestry. As part of the WTCCC2, 4134 GoDARTS type 2 diabetes cases were selected for a study of response to oral hypoglycemic agents. After quality control, 1024 cases were identified who were initiated on metformin and had a definitive metformin response (discovery cohort). The remainder of the GoDARTS cases not used for discovery were used for a secondary analysis, hemoglobin A1c (HbA1c) was examined as a quantitative trait in linear regression analyses. Genotyping in the discovery sample was done using the Affymetrix 6.0 microarray, and 705 125 single-nucleotide polymorphisms (SNPs) were analyzed. TaqMan was used for replication genotyping. A selective ataxia telangiectasia mutated (ATM) inhibitor, KU-55933, was used to study the activation of AMPK by metformin in rat hepatoma cells.

Principal Findings
Fourteen SNPs with P<1×10^-6 mapped to a 340-kb linkage-equilibrium block on chromosome 11. The most strongly associated SNP—rs11212617—had an allelic odds ratio for treatment success of 1.64 (P=1.9×10^-7). When analyzing HbA1c as a continuous trait, the same SNP was also associated with decreased HbA1c (β=−0.18, P=1.8×10^-5). The minor allele (C) had a frequency of 44%. This association was replicated in the 2 replication cohorts. The combined odds ratio across discovery and replication cohorts was 1.35 (P=2.9×10^-7) for 3920 metformin-treated patients. Each copy of the minor allele was associated with 0.18 lower absolute HbA1c (P=3.7×10^-4). The association was also consistent for the metformin mono-therapy subgroup. There was no association of the rs11212617 SNP with HbA1c, homeostatic model assessment of insulin resistance, and fasting insulin in >35 000 individuals without diabetes from the Meta-Analyses of Glucose and Insulin-Related Traits Consortium, indicating that the genotypic effect on metformin response was not related to an intrinsic effect on HbA1c.

The rs11212617 SNP associated with treatment success was in a locus containing the ATM gene. The ATM gene encodes a 370-kDa protein that is a serine/threonine protein kinase of the PIKK (phosphatidylinositol-3 kinase-related kinase) family and is known to be involved in DNA repair and cell cycle control. Individuals with ataxia telangiectasia have been found to have insulin resistance and increased risk
of diabetes; additionally, activation or inhibition of ATM has been reported to alter AMPK activation. To investigate whether ATM was the causal gene affecting treatment response, a selective inhibitor of ATM was studied in rat hepatoma cells. It was found that inhibition of ATM attenuated the phosphorylation and activation of AMPK in response to metformin. The authors concluded that ATM acts upstream of AMPK and is required for complete response to metformin.

Implications
Type 2 diabetes has been previously associated with increased risk of cancer, and metformin has been recognized as having a protective effect on cancer risk. The implication of ATM, a gene known to be involved in DNA repair and cancer, in metformin response among persons with diabetes may provide a mechanistic link between cancer and type 2 diabetes. The findings may not be of immediate clinical utility, because this gene explains only 2.5% of the variation in metformin response. Further work is needed before there are enough data to use genetic testing to guide treatment of type 2 diabetes. However, these findings suggest a new area for diabetes drug development and have established an unanticipated link between glucose homeostasis and the DNA damage response system.

Disclosures
None.
Variation in the ATM Gene May Alter Glycemic Response to Metformin
Nicole L. Glazer

Circ Cardiovasc Genet. 2011;4:210-211
doi: 10.1161/CIRCGENETICS.111.960047
Circulation: Cardiovascular Genetics is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2011 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/4/2/210

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/