Variation in the \textit{ATM} Gene May Alter Glycemic Response to Metformin

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Study Hypothesis

Metformin has been used for >50 years for the treatment of type 2 diabetes and generally is recommended as first-line therapy. However, glycemic response to the drug varies widely among patients with diabetes, and the mechanism of action of metformin has not been fully elucidated. It is known that metformin activates AMP-activated protein kinase (AMPK), but it is unknown whether AMPK is the only therapeutic target of metformin. The authors hypothesized that by using genome-wide association studies, they could clarify the mechanism of action of metformin and identify genetic variants that may predict treatment response.

How Was the Hypothesis Tested?

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 definable metformin response (discovery cohort). The remainder of the GoDARTS cases not used for discovery were used for the first-round replication (n=1783). The UK Prospective Diabetes Study was used as the second replication cohort; a total of 1113 individuals with type 2 diabetes were either randomized to metformin or treated with metformin per study protocol. The primary outcome examined was reduction of hemoglobin A1c to <7% in the first 18 months of therapy (considered treatment success). Logistic regression analyses were performed assuming an additive genetic model. As 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 2 replication cohorts. The combined odds ratio across discovery and replication cohorts was 1.35 (P=2.9×10^{-5}) for 3920 metformin-treated patients. Each copy of the minor allele was associated with 0.11 lower absolute hemoglobin A1c (P=2.9×10^{-5}). The rs11212617 SNP associated with treatment success was replicated in the 2 replication cohorts. The association was also consistent for the metformin monotherapy 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 \textit{ATM} gene. The \textit{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.
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