Researchers find genetic markers to help fight diabetes

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Translational Genomics Research Institute (TGen) scientists have identified five genetic biomarkers that could help lead to improved treatments, with fewer side-effects, for patients with diabetes.

TGen Senior Investigator Dr. Johanna DiStefano presented the findings in New Orleans on June 6, 2009, at the 69th Scientific Sessions of the American Diabetes Association.

"We identified genetic variants that may predict how well someone will respond to the common anti-diabetes drug, Actos," said Dr. DiStefano, Director of TGen's Diabetes, Cardiovascular & Metabolic Diseases Division. "The implications of these findings include determining which patients will best respond to the drug for the prevention or treatment of diabetes. In addition, this work lays the foundation for personalized medicine for patients with this disease."

Personalized medicine involves the rapid application of laboratory discoveries to therapies, depending on the individual genetic make-up of each patient.

A TGen-led team, working with scientists from the University of Southern California's Keck School of Medicine, investigated why as many as 30-40 percent of diabetes patients treated with thiazolidinediones (TZDs), such as Actos, fail to respond to the drug with the expected improvement in insulin sensitivity.

TZDs are a class of insulin-sensitizing drugs used to treat type 2 diabetes mellitus (T2DM). TZDs are agonists for the nuclear receptor peroxisome proliferator-activated receptor-g (PPARG). Although the exact mechanism by which TZDs act is not yet known, data indicate that TZDs improve insulin sensitivity by direct and indirect effects on adipose tissue and muscle. TZD therapy can significantly lower diabetes incidence in at-risk subjects, suggesting this treatment may be an effective means to prevent the disease.

Previously, TGen and Keck investigators found that genetic variations in the PPARG gene were associated with TZD metabolism and the biological effects of TZD, and thereby contribute to the therapeutic response associated with TZD. However, these variants did not fully account for the non-response rate, suggesting that other variants may contribute to TZD response.

To identify other variants that predict response to TZDs, TGen researchers performed a genome-wide analysis of 115,352 single nucleotide polymorphisms, or SNPs (a DNA sequence variation within the more than 3 billion base pairs in the human genome). In addition, the scientists also systematically screened 28 key genes involved in TZD metabolism or PPARG-stimulated pathways.

Of the markers examined, DiStefano and her team identified five critical markers that may predict response to TZD mono-therapy. These markers include variants in a key drug metabolizing gene called cytochrome P450 3A4 and a PPARG-coactivator known as PPARGC1B. Other markers were located in genes associated with PPARG function and include the protein kinase MAP2K6, a potassium inwardly-rectifying channel called KCNJ16, and the farnesoid X receptor (NR1H4).

Together, these markers predicted both response to Actos therapy and improvement in insulin sensitivity in the patients taking the drug.

Dr. DiStefano said the next steps in this research will be to characterize the functional effects of the polymorphisms and assess the effect of these variants in other patients.

"This work may help treat the right people with the right drug, design better drugs that will effectively improve insulin sensitivity for more people, and possibly safeguard against adverse side reactions seen with some members of this drug class," she said. Importantly, these findings will enable us to dissect the pharmacogenetics of TZD response, which will expand our understanding of the genetic determinants of insulin resistance and its treatment, provide critical baseline information for the development and implementation of genetic screening into the therapeutic decision making process, and lay the foundation for "individualized medicine" for patients with T2D.

Source: The Translational Genomics Research Institute