Genetic approach could help identify side-effects at early stages of drug development

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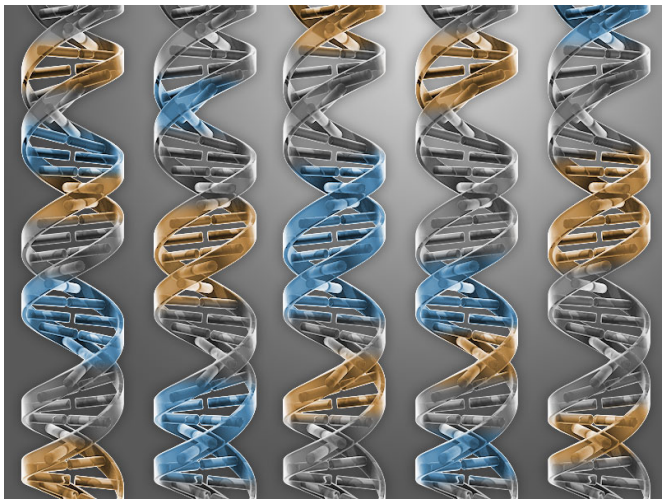

A new study harnesses genomic data to predict patients' risk of side effects from antidiabetic drugs. Credit: C. Bickel / Science Translational Medicine (2016)

An approach that could reduce the chances of drugs failing during the later stages of clinical trials has been demonstrated by a collaboration between the University of Cambridge and pharmaceutical company GlaxoSmithKline (GSK).

The technique involves identifying genetic variants that mimic the action of a drug on its intended target and then checking in large patient cohorts whether these variants are associated with risk of other conditions, such as cardiovascular disease.

When developing a new drug for market, pharmaceutical companies must not only demonstrate that it is effective at treating a particular condition, but also that the drug does not have any adverse side-effects in patients. For example, the Food and Drug Administration, which approves all new medicines for use in the USA, has defined that any new anti-diabetic medicines need to demonstrate cardiovascular safety.

However, in many cases adverse safety profiles do not become apparent until late in the drug development process, by which point millions - possibly even billions - of pounds will have been invested.

In a study published today in the journal *Science Translational Medicine*, scientists have provided a proof of concept that it is possible to use genetic analyses to demonstrate systematically at a very early stage whether a drug will alter the risk of developing other conditions.

A major class of anti-diabetic therapies are those known as glucose-lowering glucagon-like peptide-1 receptor (GLP1R)-agonists. These drugs bind to the GLP-1 receptor (which is encoded by the GLP1R gene) to increase insulin production, helping reduce levels of blood sugar. However, the cardiovascular safety, of this class of agents, including the risk of heart disease for example, remains unknown.

By analysing genetic variations in DNA encoding drug targets for type 2 diabetes and obesity in almost 12,000 individuals, the researchers identified a variant in the GLP1R gene that was associated with lower fasting glucose and a lower risk of type 2 diabetes - in other words, the variant appeared to mimic the action of the diabetes drugs. They confirmed this result in a further 40,000 individuals.

The researchers then used genetic data available through an international data-sharing consortium to study the association of that same variant with coronary heart disease in almost 62,000 individuals with coronary heart disease and over 160,000 controls. In fact, they found that the variant actually reduced the risk of heart disease. Long-term large-scale randomised controlled clinical trials to evaluate the cardiovascular safety of GLP1R-agonists are underway and results from a large trial are scheduled to be released later this month.

"This further suggests that human genetics can support the development of new therapies, and can offer insights into their safety profile early in the development process," says Dr Robert Scott from the Medical Research Council (MRC) Epidemiology Unit at the University of Cambridge, the study's first author.

Professor Nick Wareham, Director of the MRC Epidemiology Unit, added: "These findings suggest that beyond their effectiveness in treating diabetes, these drugs may have the added benefit of lowering risk of heart disease."

"Researching and developing new medicines is a lengthy, expensive and risky journey, and any insights we can gain in to the processes of the body related to disease could help improve our ability to succeed," says Dr Dawn Waterworth, joint senior author from GSK. "By pooling our resources and expertise in collaborations like this one with Cambridge University, we believe there's an opportunity to expand our knowledge of disease biology, which in turn could help reduce the risk of late-stage failures and accelerate the development of innovative new treatments for patients."

More information: Scott, R et al. A genomic approach to therapeutic target validation identifies a glucose-lowering GLP1R variant protective for coronary heart disease. *Sci Trans Med*; 2 June 2016, stm.sciencemag.org/lookup/doi/ … scitranslmed.aad3744

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