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New genetic research can significantly improve drug development

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According to a new study published in the *International Journal of Epidemiology* this week, genetic research in large-scale prospective biobank studies can significantly improve the drug development pipeline and reduce costs.

New treatments are discovered by exploring biological pathways that cause disease but can be modified by drugs. The route from the basic biology to large-scale randomized trials in humans is long and expensive – estimated at over $1.2 billion to get one product to market. In part, that costs is because the route to a successful drug is littered with those that have fallen by the wayside at various points during development. However, a study of one such unsuccessful drug has pointed to a way that could reduce costs.

Lipoprotein associated phospholipase A2 (Lp-PLA2) circulates with cholesterol in the blood and high levels are associated with increased risk of cardiovascular disease, so inhibiting Lp-PLA2 might be beneficial. Darapladib, an inhibitor of Lp-PLA2, was developed by Human Genome Sciences which GlaxoSmithKline (GSK) bought for US$ 3 billion in 2012. But two large phase III trials of darapladib funded by GSK were disappointing failures. The investment in the Lp-PLA2 inhibitor did not pay off because the biological pathway turned out to be one that caused cardiovascular disease.

Researchers at the University of Oxford and the Chinese Academy of Medical Sciences joined forces with GSK to explore whether this

disappointing result could have been predicted by using a genetic variant that mimics the drug effect. People with a non-functioning variant have lower levels of Lp-PLA2 so the idea is to see if these people have a lower risk of cardiovascular disease than those with functioning variants. In a study of over 90,000 participants in the prospective China Kadoorie Biobank (CKB) study, the association between this genetic variant and a range of cardiovascular and non-cardiovascular diseases was explored. This method is termed "Mendelian randomization" because it relies on way the play of chance determines the genetic variants inherited at conception, and allows nature to mimic randomised controlled trials.

The researchers found that people with a non-functioning genetic variant were not at lower risk of developing cardiovascular (and other non-cardiovascular) diseases – upholding the trial findings. Compared with the many steps in the traditional pathway to drug development (at a cost of several billion dollars) the availability of large scale biobanks make the cost of carrying out Mendelian randomization analyses trivial. This methodology is likely to be much more widely used to examine the causal nature of biological pathways involved in diseases before mounting large-scale trials in the future.

Study lead author Dr Iona Millwood, from the University of Oxford, said 'Our research used a genetic variant only found in East Asians, and demonstrates the value of prospective biobank studies with genetic data linked to health records, carried out in different global populations, to predict the potential benefits or harms of new drug targets.'

Professor Zhengming Chen, senior author and the principal investigator of the China Kadoorie Biobank at the University of Oxford, said 'CKB is a powerful resource. Our ongoing research includes measurement of thousands of functional genetic variants which may represent potential drug targets in different biological pathways, and we are using the same approach to assess a number of other important therapeutic targets.'

The study showed that genetics has a huge potential to improve the drug development pipeline and close collaborations between the pharmaceutical industry and academic researchers are likely to play an important role in future drug discovery and development, capitalising on the large prospective biobank studies already established.

More information: "A phenome-wide association study of a lipoproteinassociated phospholipase A2 loss-of-function variant in 90,000 Chinese adults." *International Journal of Epidemiology*; DOI: 10.1093/ije/dyw087

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