Medical Xpress

Drug repurposing study sheds light on heart disease risk

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A team led by researchers at Brigham and Women's Hospital has developed a computational technique to reveal the unknown side effects—both good and bad—of hundreds of drugs. That knowledge could help pharmacologists discover new indications for drugs already

on the market and repurpose them for other disorders. Using their unique method, the researchers discovered that two drugs commonly prescribed for non-coronary disorders may affect heart disease risk. Their findings were recently published in *Nature Communications*.

Most medications work by binding to a diseased protein target. However, previous research has shown that some can also interfere with unknown and unintended targets and biological processes. That helps explain why many drugs succeed in single-cell and animal experiments but fail in clinical trials when introduced to the more complex human body.

"The great majority of drugs are not unique to the single target for which they've been developed," said Joseph Loscalzo, MD, Ph.D., Chair of the Department of Medicine Chair at BWH, who led the study. "They may have many off-target effects—some potentially beneficial, and some adverse."

The team used archival data to examine how 700 FDA-approved medications interact with various proteins. To fully characterize off-target effects, they built maps of human protein interactomes -networks of protein-protein interactions contained in cells—using existing datasets. They located the subnetworks containing diseased proteins and drug targets unique to heart disease. They identified drugs used for non-cardiovascular disorders whose targets were very near or within the cardiovascular disease subnetworks. Then they explored health care databases containing clinical information from more than 220 million patients and identified the incidence of cardiovascular events in individuals treated with these drugs.

They found that hydroxychloroquine, an anti-rheumatic drug, was associated with lower rates of coronary artery disease. This finding raises the possibility that hydroxychloroquine could be repurposed for treating this common artery-obstructing disorder.

Conversely, they found that carbamazepine, a drug mainly prescribed for epilepsy and neuropathic pain, may increase the risk of coronary artery disease. This could mean that patients who are older, diabetic or otherwise at higher risk for coronary artery disease should consider alternative medications for such neurological conditions.

The research team investigated possible mechanisms for the relationship between these two medications and coronary artery disease risk using lab studies of human vascular cells. They next plan to fully characterize the off-target effects for more drugs and diseases. Their interactome maps and network prediction methods, along with the FDA drug target dataset they used, are open-access for other researchers to utilize.

"Until recently, there hasn't been a way to look at all possible drug targets," said Loscalzo. "Now we have the tools to do so, which can facilitate drug repurposing."

More information: Feixiong Cheng et al, Network-based approach to prediction and population-based validation of in silico drug repurposing, *Nature Communications* (2018). DOI: 10.1038/s41467-018-05116-5

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