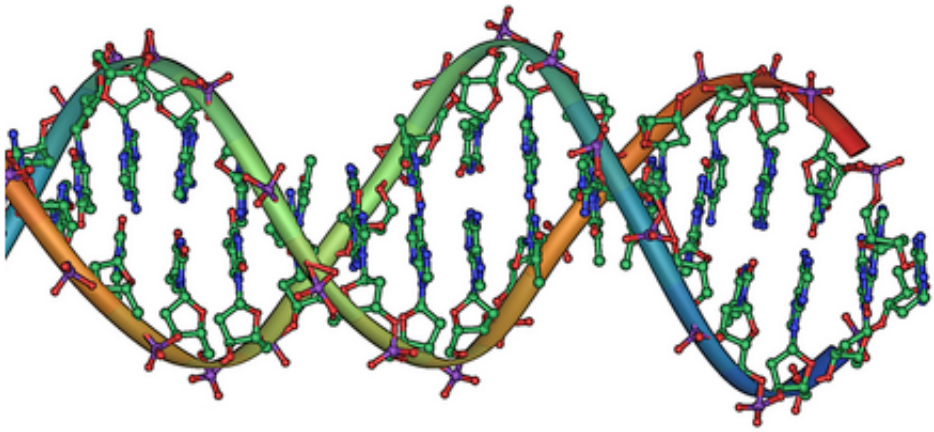
Detailed analysis of autism-associated genes finds involvement in key pathways, processes

April 7 2016



DNA double helix. Credit: public domain

A group of Massachusetts General Hospital (MGH) investigators has identified key underlying biological processes that involve some of the hundreds of genes known to contribute to the risk of autism spectrum disorders (ASDs). Several separate analyses converged on a key molecular process - the overlap of two major signaling pathways - as well as on several groups of genes that participate in that process and contribute to other conditions.

"Our pathway network analysis is the first bioinformatics study in autism to connect the dots of brain and body - of autism and accompanying medical conditions, of autism and vulnerability to environmental stress - in one investigation," says Ya Wen, PhD, a research fellow in the Department of Neurology at MGH and MassGeneral Hospital for Children (MGHfC) and lead author of the study published in the open-access journal *PLOS One*. "This coherence of results from different approaches reinforced our confidence that we were on to something fundamentally important."

While it was originally expected that variations in only a few genes would explain the development of ASDs, major databases now list hundreds of genes that have been associated with the developmental disorders, with more added frequently. The MGH research team drew on the SFARI (Simons Foundation Autism Research Initiative) Gene database, which listed more than 650 genes as relevant to ASDs at the time the study was performed. To make sense of this diversity, they used additional databases to determine the pathways in which these genes participate and generate a network based on pathway interactions.

Not only did the pathways found to be most strongly associated with ASDs have many interactions with each other, they also had overlapping associations with conditions as diverse as cancer, metabolic and neurodegenerative disorders, and heart disease. Most prominent were the calcium and MAP kinase signaling pathways - which control key cellular activities - followed by metabolic and neural pathways. Particularly intriguing was that the calcium and MAP kinase pathways overlapped in a process known to play a central role in a large range of biological functions, the activities of which - when abnormal - are known to be associated with cancer, metabolic and neural disorders, and heart disease.

"As the science of autism has moved from looking for a few genes to

finding hundreds, we have been challenged to explain how so many different genes could contribute to such a distinctive condition," says Martha Herbert, MD, PhD, director of the TRANSCEND (Treatment Research and NeuroSCience Evaluation of Neurodevelopmental Disorders) research lab in the MGH/MGHfC Department of Neurology, senior author of the *PLOS One* report and an assistant professor of Neurology at Harvard Medical School. "Our pathway analyses show that the diversity of genes may be linked by a smaller number of impactful pathways, and we hope our findings contribute to increasing the coherence and power of autism research and treatment."

The authors add that a better understanding of how pathways interact may lead to more successful strategies for treating and even preventing ASDs in the future. "Many present treatments attempt to control or reduce particular symptoms of autism, but this study suggests that targeting core biological processes may be a more efficient strategy," says Wen. "Addressing a core process that generates a spectrum of symptoms may give you a shot at affecting all of those symptoms at ones. This is just a first step along what we hope will be a path to better care, but it is an important one."

More information: *PLOS One*, dx.doi.org/10.1371/journal.pone.0153329

Provided by Massachusetts General Hospital