Researchers develop new approach to study the genetics of human disease

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Credit: University of Chicago Medical Center

Many heritable immune diseases such as rheumatoid arthritis and blood-cell related traits derive from critical proteins not being made or not functioning correctly. But exactly how a person's genes, the regulation of these genes and how the resulting proteins interact to cause disease is not widely understood.

In a new paper published in *Nature Genetics*, University of Chicago researchers discovered that a form of RNA chemical modification, N6-Methyladenosine (m6A), plays an important role in human disease heritability.

By studying immune cells, they found that abnormalities in m6A levels may correlate with autoimmune diseases and blood cell-related traits. By understanding this relationship, there is an opportunity to change this process and treat inherited human diseases.

"This is a very modern topic in the field of genetics and we took a different approach than other studies," said Zijie Zhang, a UChicago graduate student and lead author of the paper. "Many studies focus on genetic variation's role in transcription (turning DNA into messenger RNA), whereas our study demonstrates that genetic variation is also involved in m6A mediated post-transcription regulation such as translation (turning messenger RNA into proteins)."

Through the analysis of m6A data using a statistical methodology called QTL mapping, which links phenotypic traits to genotypic variations, researchers found that m6A was as impactful in modulating disease susceptibility as it was in RNA splicing and that m6A is about half as impactful as gene expression.

By studying the mechanisms of m6A related to disease, researchers could be one step closer to developing treatments for these diseases. Genetic modifications to m6A could mean that mRNA isn't translated into necessary proteins. Future therapies can target this pathway to tune the m6A level of disease susceptible genes without replacing the genetic code that alters the functioning of m6A.

Seeing m6A's association with the heritability of disease contributes to a larger understanding within the scientific community that

posttranscriptional regulation plays an important role in common diseases.

"We do not yet know the mechanisms of the genetic variants that are associated with common diseases," said Xin He, Ph.D., Assistant Professor of Human Genetics and co-senior author of the paper. "Our paper provides some examples where genetic variations of immune traits change m6A levels in specific genes, suggesting possible paths from genotypic to phenotypic variations. This approach can point to potential therapeutical targets."

Researchers also discovered the m6A works in both prompting and suppressing mRNA translation while previous works studying a single m6A reader protein (e.g. YTHDF1) only focused on the translation promotion role of m6A. "We found that m6A has a heterogeneous effect on translation that works differently depending on the context, which adds new insights to the widely appreciated model that m6A promotes translation efficiency and mRNA decay via interactions with reader proteins," said Zijie Zhang.

Additionally, this study's methods of statistical analysis lay the foundation for other teams to take a similar approach to understand other diseases. For example, according to Xin He, the same methodology could be used to study brain tissue to see if m6A plays a role in neuropsychiatric diseases.

"These are novel methods that can be broadly applied to study human tissues directly, so it is a very exciting study," said co-senior author Chuan He, Ph.D., John T. Wilson Distinguished Service Professor in the Department of Chemistry and the Department of Biochemistry and Molecular Biology.

More information: Zijie Zhang et al. Genetic analyses support the

contribution of mRNA N6-methyladenosine (m6A) modification to human disease heritability, *Nature Genetics* (2020). DOI: 10.1038/s41588-020-0644-z