International study reports the impact of genetics on epigenetic factors
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Understanding what causes epigenetic variation could be a step closer thanks to a new atlas of genetic effects on epigenetic factors. The atlas, which has been established by an international consortium including researchers from the University of Exeter, will enable scientists to learn more about the mechanisms underpinning gene regulation.

Epigenetic variation exists, but it is unclear what causes this variation—is it genetic or is it the environment? It is also unclear how genetic differences that occur between individuals affect our epigenomes. The atlas of genetic effects on DNA methylation (DNAm), by the Genetics of DNA Methylation Consortium (GoDMC) of 50 universities and institutes and more than 150 scientists, including the University of Bristol, University of Exeter Medical School, King’s College London and Leiden University Medical Center, is published in *Nature Genetics*.

The analysis focused on the natural differences between individuals in their DNAm levels across the genome. DNAm plays a central role in gene regulation. It helps to define how cells respond to environmental signals, and ultimately, contributes to health or susceptibility to disease. However, the amount and the effects of differences in DNAm from one person to another is poorly understood.

A powerful avenue into researching the biological consequences of changes in DNAm levels is to systematically compare DNA sequence variants to DNAm levels. GoDMC has completed the largest genetic study of DNAm to date by scanning for correlations between ten million genetic variants and 420,000 DNAm sites across the genome, resulting in a database of >270,000 independent associations. This means that almost half of all DNAm sites in the genome are to some extent influenced by genetic factors.

The international consortium analyzed 32,851 participants collected from 38 studies across the world. By providing a world-wide platform for collaboration and combining genetic and epidemiological expertise, the scientists of GoDMC have established a large resource of genetic effects on DNAm and how this atlas can be used to understand the genetic basis of DNAm variation. The atlas has already been used for a wide range of other research projects.

The newly developed database has been used to search for instances of DNAm sites causally relating to 100 clinical characteristics and diseases. Conversely, the study estimated the causal influences of these clinical characteristics and diseases on DNAm levels across the genome. These comparisons highlight that DNAm is unlikely to have a big role in causing disease, but they open the door to a range of further research. For example, this work suggests that understanding of DNAm variation between individuals and its influence on health and disease could be improved by studying other regulatory regions of the genome or other cell types.

Professor Jonathan Mill, of the University of Exeter, who was one of the lead researchers on the project, said, “This was a huge collaborative effort..."
involving scientists from around the world. The study has enabled us to explore how genetics and epigenetic interact, generating an unrivaled dataset that can be used to elucidate causal mechanisms in health and disease."

Dr. Josine Min, Research Fellow in Genetic and Epigenetic Epidemiology at the University of Bristol and GoDMC coordinator, said, "Understanding differences in genetic regulation between tissues that comprise diverse cell-types is complex. Our large-scale comparison of DNAm and genetics across blood, brain and adipose tissue highlighted that long distance regulation is largely shared across tissues but that local regulation is more tissue specific. Improved understanding of how different tissues develop and respond to disease will help to advance our understanding of the causes of disease."


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Provided by University of Exeter