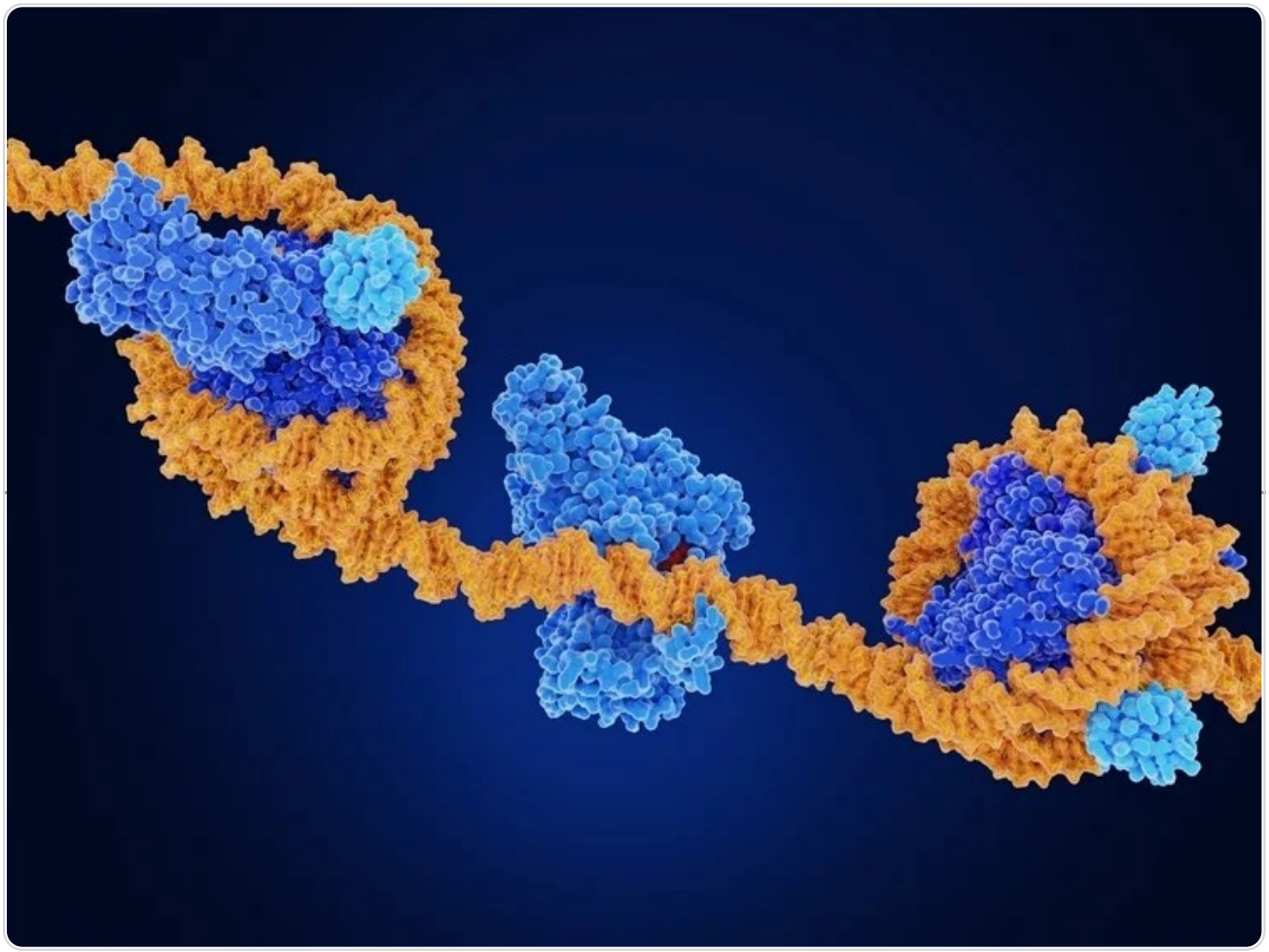
Cannabis use alters DNA methylation, with implications beyond smoking effects

By Dr. Chinta Sidharthan

Nov 8 2023

Reviewed by Susha Cheriyedath, M.Sc.

In a recent study published in the journal *Molecular Psychiatry*, a team of researchers conducted a large-scale meta-analysis consisting of an epigenome-wide association study to understand whether lifetime use of cannabis was linked to deoxyribonucleic acid (DNA) methylation observed in peripheral blood.



Study: Trans-ancestry epigenome-wide association meta-analysis of DNA methylation with lifetime cannabis use. Image Credit: Juan Gaertner / Shutterstock

Background

With an increasing number of states in the United States (U.S.), as well as

countries across the world legalizing the medicinal use of cannabis, cannabis usage has become exceedingly prevalent. However, while the therapeutic benefits of cannabis through medicinal use have been well-studied, its recreational use also raises numerous concerns, especially regarding problems associated with addiction, cognitive deficits, and mental health disorders such as depression, anxiety, psychosis, mania, and schizophrenia.

DNA methylation is an indicator of the impact of environmental factors on health, and some forms of DNA methylation due to environmental factors are long-lasting, while others are transient. It occurs when a methyl group gets added to the fifth carbon of cytosine in regions with cytosine and guanine (CpG) repeats. Studies have reported that cigarette smoking results in both persistent and transient DNA methylation at CpG sites across the genome. DNA methylation patterns in specific genes have also been observed in groups such as adolescents who frequently use cannabis and patients who are dependent on cannabis.

About the study

In the present study, the team built on the methods from their previous study, where they performed the first epigenome-wide association study using peripheral blood samples and investigated a large study population consisting of seven cohorts of individuals of different ancestries. They examined the association between lifetime cannabis use and DNA methylation patterns while adjusting for factors such as age, sex, technical covariates, blood cell proportions, and cigarette smoking behavior.

The data was obtained from seven cohorts that participated in the study, spanning diverse study groups such as twins, older adults, parents and children, and adult twins. The final study population comprised 4,190 individuals who reported using cannabis in their lifetime and 5,246 individuals who had never used cannabis in their lifetime, constituting a total of 9,436 participants. Cannabis use was characterized based on reports by the participants or parents, and an individual with a minimum of one cannabis use event before the collection of peripheral blood samples was defined as an ever-user.

DNA methylation was measured in the peripheral blood samples, and the β-values, which is the percentage of methylated DNA at the targeted CpG sites,

were calculated. The association between lifetime cannabis use and DNA methylation levels was tested using linear models or a generalized estimating equations model in cohorts where the participants were related. The epigenome-wide association study analyses were stratified according to the European-American and African-American genetic ancestry groups, and the analyses were adjusted for sex, age, cigarette smoking, and blood cell type estimates.

The meta-analysis summarized the ancestry and cohort-specific results from the epigenome-wide association study, and statistical analyses were conducted to assess. The methylation score, which is the weighted sum of the CpG sites significantly linked to cannabis use, was also calculated. Additionally, DNA methylation correlations between whole blood and regions of the brain, such as the prefrontal cortex, cerebellum, superior temporal gyrus, and entorhinal cortex were examined.

Results

The results reported that four CpG sites showed significant associations with cannabis use, and these included CpG sites in the disintegrin and metalloprotease 12 (*ADAM12*) and alpha-actinin 1 (*ACTN1*) genes and near the adhesion G protein-coupled receptor F1 (*ADGRF1*) gene and long noncoding ribonucleic acid (RNA) *LINC01132*.

The basic model of the epigenome-wide association study indicated that cannabis use was associated with DNA methylation in CpG sites that largely overlapped with those linked to cigarette smoking. However, adjusting for cigarette smoking behavior identified another CpG site associated with cannabis use in the apolipoprotein B receptor (*APOBR*) gene.

The five genes containing DNA-methylated CpG sites associated with cannabis use have significant roles in various health outcomes. *LINC01132* functions as an oncogene and is linked to malignancy in hepatocellular carcinoma and ovarian cancer, although cannabis use has been reported to lower the incidence of hepatocellular carcinomas. Genetic variation in the *ACTN1* gene, which encodes the cytoskeletal protein that binds actin fibers to cell membranes, has been linked to various diseases such as Bowen disease, Angelman syndrome, lupus erythematosus, and congenital macrothrombocytopenia, as well as coronavirus disease 2019 (COVID-19).

Conclusions

Overall, the findings reported substantial DNA methylation changes in CpG sites across five genes that play significant roles in health and disease. While four of these CpG sites overlap with those associated with cigarette smoking, cannabis use by itself is also linked to DNA methylation in one gene. The results highlight the utility of DNA methylation as a tool to understand the interactions between environmental factors and genetics and emphasize the need for further research on the impact of cannabis use on health outcomes.

Journal reference:

- Fang, F., Quach, B., Lawrence, K. G., Dongen, van, Marks, J. A., Lundgren, S., Lin, M., Odintsova, V. V., Costeira, R., Xu, Z., Zhou, L., Mandal, M., Xia, Y., Vink, J. M., Bierut, L. J., Ollikainen, M., Taylor, J. A., Bell, J. T., Kaprio, J., & Boomsma, D. I. (2023). Trans-ancestry epigenome-wide association meta-analysis of DNA methylation with lifetime cannabis use. *Molecular Psychiatry*. https://doi.org/10.1038/s4138002302310w, https://www.nature.com/articles/s41380-023-02310-w

Written by

Dr. Chinta Sidharthan

Chinta Sidharthan is a writer based in Bangalore, India. Her academic background is in evolutionary biology and genetics, and she has extensive experience in scientific research, teaching, science writing, and herpetology. Chinta holds a Ph.D. in evolutionary biology from the Indian Institute of Science and is passionate about science education, writing, animals, wildlife, and conservation. For her doctoral research, she explored the origins and diversification of blindsnakes in India, as a part of which she did extensive fieldwork in the jungles of southern India. She has received the Canadian Governor General's bronze medal and Bangalore University gold medal for academic excellence and published her research in high-impact journals.