Study explores role of epigenetics, environment in differing Alzheimer's risk between Black and white communities

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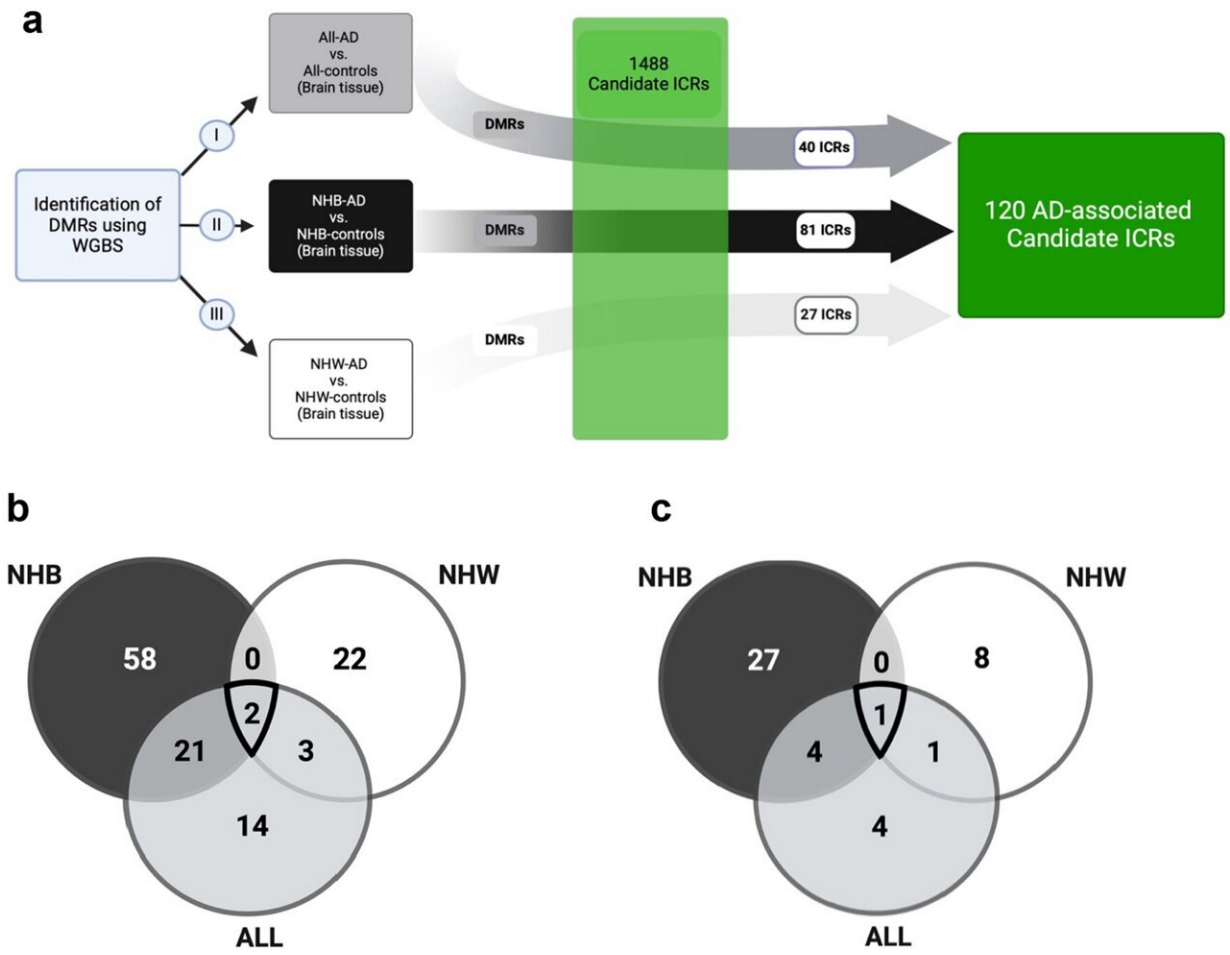

DNA methylation of imprint control regions associated with Alzheimer's disease in non-Hispanic Blacks and non-Hispanic Whites. Credit: *Clinical Epigenetics* (2024). DOI: 10.1186/s13148-024-01672-4

A study from North Carolina State University has found that environmentally caused alterations to specific areas of the genome—known as imprint control regions—during early development may contribute to the risk of developing Alzheimer's disease, and that Black people may be more affected than white people. The work adds to our understanding of the ways in which environmental factors can contribute to genetic alterations and disease susceptibility.

The study is published in the journal *Clinical Epigenetics*.

"In terms of genetics and disease, I always think of Dr. Kenneth Olden's analogy: genetics loads the gun and the environment pulls the trigger," says Cathrine Hoyo, professor of biological sciences at NC State and co-corresponding author of the research.

"In fact, the Institute of Medicine has estimated that epigenetic response to the environment –how our genes respond to the environment—contributes between 70% to 90% of chronic disease risk. And we know that in the case of Alzheimer's disease, only about 5% of cases are familial, or inherited.

"We also know that the risk of developing non-familial, or sporadic, Alzheimer's differs according to race—Black people have twice the incidence of white people," Hoyo continues. "So we wanted to see if we could identify stable epigenetic features—parts of the epigenome that are unlikely to change once established—that distinguished Alzheimer's brains from those without the disease."

Specifically, the research team used the imprintome—the imprint control regions (ICRs) in the human genome that regulate the expression of imprinted genes—to identify stable epigenetic features that distinguished people with Alzheimer's disease from those without.

Imprinted genes differ from other genes because only one parental copy of an imprinted gene is active. The other copy is methylated, or silenced, early in development. Additionally with these genes, the methylation marks that control their expression are susceptible to environmental influences.

"With imprinted genes, there isn't a backup copy in the event of mutation," says Randy Jirtle, professor of epigenetics at NC State and co-corresponding author of the research. "ICRs control the expression of these genes—in other words, they tell imprinted genes where, when and how to work through DNA methylation. And these methylation marks in ICRs don't normally change unless altered early in development, either at conception or shortly thereafter."

For the study, the team had brain tissue samples from 17 donors—eight normal brains and nine with Alzheimer's. Each group was divided between non-Hispanic white and non-Hispanic Black donors (the Alzheimer's group had five samples from Black donors and four from white donors).

The team sequenced the entire genome for each sample, then looked for ICRs in the Alzheimer's brains that were either over- or under-methylated compared to the healthy brains.

They found 120 differently methylated ICRs in the Alzheimer's brains. Forty were found in the combined Black and white populations; however, 81 ICRs were found only in the Black population, and 27 were found only in the white population.

The differently methylated ICRs common to both populations are associated with (MEST/MESTIT1), a paternally expressed imprinted gene, and NLRP1, a predicted imprinted gene involved in brain inflammation.

"The importance of finding the common ICRs is that it could help us develop universal tests for potential disease markers," says Hoyo. "But it was very puzzling to discover that the Black population had almost three times as many affected ICRs as the white population.

"When you see that level of difference, and you know that the changes you're finding are likely caused early by environmental interactions, one possible explanation is that there are unique or different stressors in that population, and those epigenetic effects are being passed along."

The researchers hope the work could lead to testing and targeted early interventions to prevent Alzheimer's disease.

"We know that targeted prevention over long periods can alter risk," Hoyo says. "So if you can alert people early on about their risk and apply targeted interventions, you could prevent disease onset."

"Epigenetics is the science of hope," Jirtle says. "You can't necessarily reverse genetic mutations, but when you know disease risks result from changes in the epigenome you can potentially negate them."

More information: Sebnem E. Cevik et al, DNA methylation of imprint control regions associated with Alzheimer's disease in non-Hispanic Blacks and non-Hispanic Whites, *Clinical Epigenetics* (2024). DOI: 10.1186/s13148-024-01672-4

Provided by North Carolina State University