Early lead exposure affects gene expression throughout life

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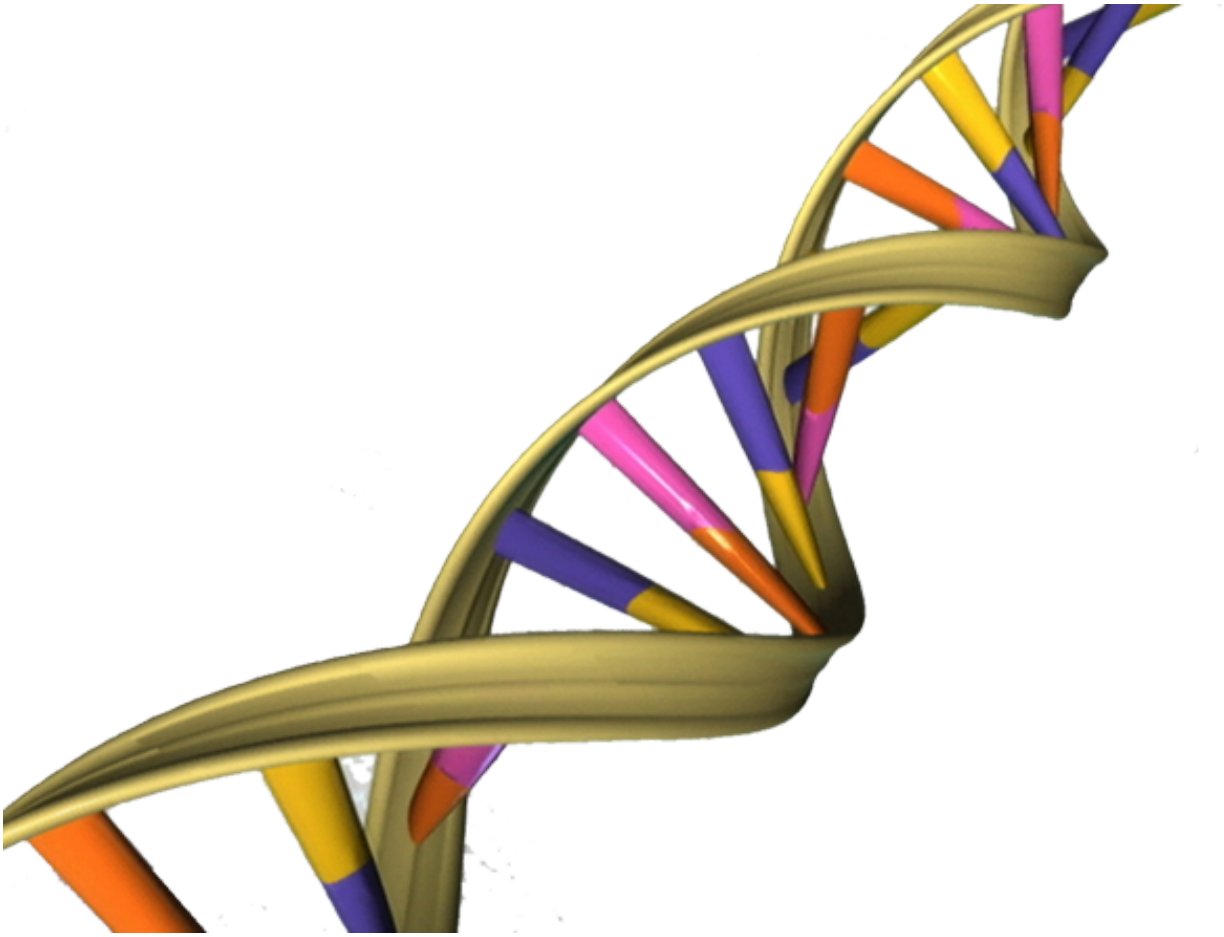

A depiction of the double helical structure of DNA. Its four coding units (A, T, C, G) are color-coded in pink, orange, purple and yellow. Credit: NHGRI

A team of researchers led by North Carolina State University biologists Cathrine Hoyo and Randy Jirtle have found links between lead exposure in children and epigenetic alterations in regulatory regions of genes that are imprinted and known to be critical in growth regulation and brain development. These alterations seem to persist into adulthood, with more profound effects in males. Their study sheds more light on the long-term effects of early lead exposure on DNA and may help to develop therapies to treat or reverse the damage.

Along with colleagues Kim Dietrich of the University of Cincinnati, Yue Li of Duke University, and NC State's David Skaar, the team looked at data collected from 105 participants in the Cincinnati lead study, which measured lead in children from birth to age 6 and a half. They followed up with the now-adult participants and took blood samples, which were sequenced for DNA methylation – data spanning 36 years.

"We now have the first human evidence for an association between early lead exposure and three aberrantly methylated regulatory regions of imprinted genes," says Hoyo. "But from a public health perspective, the results are very exciting because we can begin to think about identifying potential biological markers for early exposure to lead and other toxins in the environment."

The team spent several years pinpointing regulatory regions within DNA that may link early lead exposure to specific diseases, characterizing 22 of these regions to date. With this study, researchers looked at the 22 regions to see if lead exposure affected DNA methylation, the process that controls how a gene is expressed, essentially determining whether or not it is switched on or off. When methylation is altered, genes are either turned off (or silenced) or they are more active than they normally would be.

The team found three imprinted genes whose expression was affected in

adulthood by lead exposure from birth to 6 and a half years of age: PEG3, IGF2/H19 and PLAGL1/HYMAI. For PEG3 and IGF2/HI9, methylation decreased. The effects were sex-specific: decreased methylation for PEG3, which is associated with fetal development, affected males more than females, while the opposite was true for IGF2/H19. PLAGL1/HYMAI methylation, which increased, was not sex-specific.

Additionally, they found that increased blood levels of lead later in postnatal development did not seem to have any other effects on the regulatory regions – the methylation changes occurred during the first 12 months, even as lead exposure continued to increase over the study period.

"Genes are like computers with both hardware and software," says Jirtle. "Most scientists have been studying the hardware, which is the genetic sequence, without looking at the software, which is the regulatory layer that alters how that gene is expressed. This study gives us a first look at how the software may be affected by early exposure to lead."

Hoyo and her team plan to continue investigating possible connections between lead exposure, gene expression and disease. "The dysregulated genes we identified in this study seem to be highly malleable, especially during prenatal development and early childhood. This raises the possibility that we could nudge them back toward normal if we could therapeutically target them at the right stage of development."

The research appears online in *Environmental Health Perspectives.*

More information: "Lead Exposure during Early Human Development and DNA Methylation of Imprinted Gene Regulatory Elements in Adulthood." *Environ Health Perspect*; DOI: 10.1289/ehp.1408577

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