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Biomarking Time

Methylome modifications offer new measure of our “biological” age

Women live longer than men. Individuals can appear or feel years younger – or older – than their chronological age. Diseases can affect our aging process. When it comes to biology, our clocks clearly tick differently.

In a new study, researchers at the University of California, San Diego School of Medicine, with colleagues elsewhere, describe markers and a model that quantify how aging occurs at the level of genes and molecules, providing not just a more precise way to determine how old someone is, but also perhaps anticipate or treat ailments and diseases that come with the passage of time.

The findings are published in the November 21 online issue of the journal *Molecular Cell*.

“It’s well known that people age at different rates,” said Kang Zhang, MD, PhD, professor of ophthalmology and human genetics at the Shiley Eye Center and director of the Institute for Genomic Medicine, both at UC San Diego. “Some people in their 70s look like they’re in their 50s, while others in their 50s look like they’re in their 70s.”

However, identifying markers and precisely quantifying the actual rate of aging in individuals has been challenging. For example, researchers have looked at telomeres – repeating nucleotide sequences that cap the ends of chromosomes and which shorten with age – but have found that other factors like stress can affect them as well.

In the new *Molecular Cell* paper, Zhang and colleagues focus on DNA methylation, a fundamental, life-long process in which a methyl group is added or removed from the cytosine molecule in DNA to promote or suppress gene activity and expression. The researchers measured more than 485,000 genome-wide methylation markers in blood samples of 656 persons ranging in age from 19 to 101.

“It’s a very robust way of predicting aging,” said Zhang, one that was subsequently validated on a second sampling of several hundred blood samples from another cohort of human individuals.

The scientists found that an individual’s “methylome” – the entire set of human methylation markers and changes across a whole genome – predictably varies over time, providing a way to determine a person’s actual biological age from just a blood sample.

“It’s the majority of the methylome that accurately predicts age, not just a few key genes,” said co-senior author Trey Ideker, PhD, a professor of medicine and chief of the Division of Medical Genetics in the UC San Diego School of Medicine and professor of bioengineering in the Jacobs School of Engineering. “The methylation state decays over time along the entire genome. You look in the body, into the cells, of young people and methylation occurs very distinctly in some spots and not in others. It’s very structured. Over time, though, methylation sites get fuzzier; the boundaries blur.”

They do not, however, blur at the same rate in everybody. At the molecular level of the methylome, the researchers said it was clear that individual bodies age at varying rates, and even within the same body, different organs age differently. Moreover, cancer cells age differently than their surrounding normal cells. The findings, according to the study authors, have broad practical implications. Most immediately, they could be used in forensics to determine a person’s age based only upon a blood or tissue sample.

More profoundly, said Zhang, the methylome provides a measure of biological age – how quickly or slowly a person is experiencing the passage of time. That information has potentially huge medical import. “For example, you could serially profile patients to compare therapies, to see if a treatment is making people healthier and ‘younger.’ You could screen compounds to see if they retard the aging process at the tissue or cellular level.”

Ideker said assessing an individual’s methylome state could improve preventive medicine by identifying lifestyle changes that might slow molecular aging. He noted, however, that much more research remains to be done.

“The next step is to look to see whether methylation can predict specific health factors, and whether this kind of molecular diagnosis is better than existing clinical or physical markers. We think it’s very promising,” Ideker said.

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