

Epigenetic Clocks May Only Be Scratching the Surface of Aging

UC San Diego researchers uncover a pivotal link between genetic mutations and epigenetic changes, reshaping our understanding of aging

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Aging has always been a complex puzzle for scientists, with two dominant theories vying for prominence: the random accumulation of genetic mutations and predictable epigenetic changes. Now, researchers at the University of California San Diego School of Medicine have uncovered a surprising connection between these explanations. Their groundbreaking findings, published in ***Nature Aging***, suggest that aging might not be as straightforward as we thought—and our strategies to combat it may need a rethink.

Epigenetic modifications, often referred to as the "epigenetic clock," have become a key tool for measuring biological aging. However, according to this new study, they may be more of a symptom

than the root cause of aging. “Major research institutions and companies are betting on turning back the epigenetic clock as a strategy to reverse the effects of aging,” said Trey Ideker, Ph.D., co-corresponding author and professor at UC San Diego. “But our research suggests this may only address the surface, not the underlying cause.”

The Battle Between Mutations and Modifications

For years, scientists have debated the role of DNA in aging. The somatic mutation theory posits that random mutations—permanent changes in DNA—accumulate over time, causing the body to age. On the other hand, the epigenetic clock theory suggests that aging is driven by specific chemical modifications to DNA that alter gene expression without changing the underlying sequence. These modifications are reversible, making them an attractive target for anti-aging therapies.

Yet, a key question has lingered: What drives these epigenetic changes? To find answers, the UC San Diego team analyzed data from over 9,300 patients through the Cancer Genome Atlas and Pan-Cancer Analysis of Whole Genomes. Their analysis revealed a startling pattern: mutations were predictably linked to changes in DNA methylation, a type of epigenetic modification. Remarkably, a single mutation could trigger a cascade of epigenetic changes across the genome, far beyond its original site.

“Epigenetic clocks have been around for years, but we’re only now beginning to understand why they tick in the first place,” said Zane Koch, the study’s first author and a Ph.D. candidate in bioinformatics. “Our study demonstrates for the first time that epigenetic changes are intricately and predictably tied to random genetic mutations.”

Rethinking Anti-Aging Strategies

This discovery has profound implications for how we approach aging. If mutations are the primary driver of aging and epigenetic changes merely track their effects, reversing aging may be far more challenging than previously believed. Steven Cummings, M.D., co-corresponding author and executive director of the San Francisco Coordinating Center, reflected on the paradigm shift: “This moves us away from viewing aging as a programmed process and toward understanding it as a result of random, cumulative changes over time.”

The findings raise new questions about the efficacy of current anti-aging therapies, many of which focus on resetting the epigenetic clock. “If mutations are the root cause of these changes, then therapies targeting epigenetics might only scratch the surface,” Ideker added.

The Road Ahead

While the study marks a significant breakthrough, the authors caution that more research is needed to fully map the relationship between somatic mutations and epigenetic changes in aging. Still, the work opens new doors for understanding the aging process and could inspire innovative strategies to prevent or slow it.

For now, the fight against aging continues—but with a sharper focus on uncovering its deepest, most elusive mechanisms.

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