

New Study Links Epigenetic Changes to Genetic Mutations

There may be negative implications for epigenetic therapies.



By **Arkadi Mazin** Jan 21, 2025



A new paper published in *Nature Aging* suggests that **somatic mutations cause significant remodeling of the epigenetic landscape**. The findings might be relevant to future anti-aging interventions [1].

The genome and the epigenome

Genomic instability and epigenetic alterations are two of the hallmarks of aging [2]. The former occurs in somatic cells due to replication errors and stressors such as radiation and reactive oxygen species. DNA mutations can be relatively benign, but they can also impair cellular function, which might contribute to age-related disorders in various ways. The ultimate bad outcome of mutations in a single cell is, of course, cancer.

Epigenetic alterations are different. One type of them, methylation, involves a methyl group being added to or removed from a nucleotide in the DNA molecule, most often a cytosine that is followed by a guanine in the DNA sequence, with the two linked by a phosphate bond (which is why such sites are called CpG). CpG methylation is an important regulator of gene expression.

While the exact role of somatic mutations in aging is not entirely clear [3], CpG methylation is so strongly correlated with aging that it has formed the basis for epigenetic aging clocks, which have become increasingly popular over the last decade. However, what if mutations and epimutations are causally connected? A new study coming from the University of California suggests that this might be the case.

Building a mutation clock

The scientists note that at least one mechanism linking methylation and mutations has been known for a while: when a CpG site is methylated, the cytosine becomes more prone to spontaneous deamination, leading to its conversion into thymine. Since cellular DNA repair machinery does not always correct this change, CpG sites are common mutation hotspots. Conversely, if a mutation alters or eliminates a CpG site, it can prevent future methylation at that location.

Using tissue samples that had both mutation and methylation data available, the researchers identified several types of interaction between somatic mutations and DNA methylation. While they mostly used cancerous tissues, they also made an effort to validate their findings in healthy tissues.

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First, the researchers confirmed that mutated CpG sites were methylated less often than non-mutated sites, which concurs with the known data. However, they also found that such mutations created atypical methylation patterns in the sections of the genome surrounding the mutation site, sometimes for tens of thousands of base pairs. This was observed in all tested tissue types.

The effect size in non-cancerous tissues, however, was substantially lower than in cancerous ones. In the latter, abnormal methylation patterns were found around 15.5% of mutated sites, while in the former, the number was 8%, and the disturbances' extent was about 1,000 base pairs from the mutation site.

Having established this correlation, the researchers wanted to see whether mutation patterns can predict biological age, just like methylation clocks do. They constructed a proprietary clock based on the profile of somatic mutations, including the counts of mutations in the vicinity of the CpG sites on which the methylation clock was based.

The methylation clock won the day, showing higher accuracy in predicting chronological age, but the mutation clock was predictive as well (Pearson correlations of $r=0.83$ and $r=0.67$, respectively). Predictions from the two clocks were also correlated across individuals. This correlation held for three previously published clocks: Horvath, PhenoAge, and Hannum.

The researchers validated their findings in a smaller number of samples from non-cancerous tissues. Here, both clocks were more predictive of chronological age (which is to be expected, since cancer introduces genomic instability and disrupts normal epigenetic patterns), but the mutation clock was still substantially behind the methylation clock. The researchers concluded that somatic mutations explain more than 50% of variation in methylation age across individuals.

What does it mean for fighting aging?

Dr. Trey Ideker of UCSD, the leading author of the study, gave us a comment:

What our paper shows is that epigenetic clocks can be largely explained by underlying DNA mutations. We think this is a pretty important finding since so much investment is currently being placed in epigenetic clocks – not only as a quantitative measurement of age, but as a means of reversing it. Our study suggests that current efforts to reverse or stabilize epigenetic changes will need to seriously contend with the underlying accumulation of DNA mutations, an area that has received comparatively less attention. On the other hand, perhaps it is worth ‘doubling down’ on treatments that slow the accumulation of DNA mutations in the first place, such as caloric restriction/dieting and certain anti-aging drugs.

The results might be especially relevant to cellular reprogramming, in which cells are being either fully de-differentiated to a pluripotent state or rejuvenated using certain reprogramming factors. Cellular reprogramming is accompanied by a considerable remodeling of the epigenetic landscape. One possibly relevant question is what if, following reprogramming, the underlying mutations cause this landscape to once again become aberrant?

“Yes, this would be one concern,” Ideker noted. “Another is that the epigenetic changes are largely not causal for aging at all, and that aging is related more directly to the mutations themselves and how they disrupt protein expression, structure and function. Essentially, what our paper has done is to open up all of these new questions.”

João Pedro de Magalhães, professor at the University of Birmingham, who was not involved in this study, said, “It’s a very interesting paper, suggesting that mutations may contribute or to some degree explain epigenetic changes, including in the context of epigenetic clocks. They show that somatic mutations with age correlate with methylation changes, which is an important new observation.”

However, he also had some reservations: “The obvious limitation of the study is that it employs data from cancer patients, including mostly from tumor samples – though some noncancerous tissues were also used. Therefore, validating these findings in normal tissues is imperative to assess the relevance of somatic mutations to epigenetic aging changes.”

One company that chose to go after the particularly hard target of fixing somatic mutations is Matter Bio. Its co-founder and CSO, Dr. Sam Sharifi, who was not involved in this study, commented:

While epigenetic clocks have attracted considerable attention as markers of biological aging, they may only reflect downstream changes triggered by a deeper, more permanent force – cumulative DNA damage. This article sheds a fascinating light on the interplay between genetic and epigenetic changes and opens the door to a purely mutation-based clock. It is still early, but once this technology matures, it could provide a more robust measure for age, given the permanent nature of DNA mutations and their steady accumulation with age.

The findings of this study are also potentially relevant to the information theory of aging promoted by Dr. David Sinclair of Harvard. It postulates that epigenetic changes are an upstream cause of aging due to loss of information on how the cell should function; therefore, aging can largely be reversed by restoring this information via cellular reprogramming or other, yet to be discovered, techniques.

“This study provides compelling evidence that epigenetic changes could not only be connected to but actually be downstream of somatic mutations,” Sharifi said. “This means that the changes in epigenetic information could be consequences of genetic information loss. Unlike methylation marks, which are relatively malleable and can be experimentally reset, DNA mutations are permanent. A big question is: are both epigenetic and genetic loss of information due to upstream processes such as DNA damage, which accumulates during aging? Critically, the article’s findings raise the important notion that targeting epigenetic states alone might not suffice to reverse aging if the underlying mutational burden is driving those epigenetic shifts in the first place.”

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Literature

- [1] Koch, Z., Li, A., Evans, D. S., Cummings, S., & Ideker, T. (2025). Somatic mutation as an explanation for epigenetic aging. *Nature Aging*, 1-11.
- [2] López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2023). Hallmarks of aging: An expanding universe. *Cell*, 186(2), 243-278.
- [3] Chatsirisupachai, K., & de Magalhães, J. P. (2024). Somatic mutations in human ageing: New insights from DNA sequencing and inherited mutations. *Ageing Research Reviews*, 102268.