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DNA labels predict mortality

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Various chemical modifications in the genome determine whether genes are read or deactivated. Methyl labels in the DNA play a key role in this "epigenetic" regulation of gene activity. Life style and environmental factors influence the methylation in the genome. Scientists have already well documented links between the methylation status of specific positions in the genome and cancer as well as other diseases.

Looking beyond individual diseases: What does the methylation status in the DNA reveal about a person's health, his or her susceptibility to disease or, in short, an individual's mortality risk? Scientists in the team of Hermann Brenner from the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) in Heidelberg, in collaboration with colleagues from the Saarland Cancer Registry and the Helmholtz Research Center for Environmental Health in Munich, have now pursued this question.

In their present study, the researchers investigated the cases of 1,900 participants of two epidemiological studies called ESTHER and KORA. They used DNA from blood cells as the basis of their investigation. All study subjects were older adults and had provided blood samples when they entered the study. This was up to 14 years ago and many of them had died since then.

Methyl groups are only attached to a certain combination of DNA building blocks called CpGs. For almost 500,000 of these positions, the researchers analyzed whether their methylation levels revealed a statistical link to survival. After rigorous statistical review, it finally

boiled down to 58 CpGs that showed a strong correlation between methylation status and mortality.

Smoking leaves the strongest epigenetic tracks

These 58 CpGs were all located in genomic regions for which an association with various diseases is well documented. Interestingly, 22 of the 58 CpGs were identical with methylation positions that Brenner and colleagues had recently found in a study on the epigenetic impacts of smoking*. Of all health risk factors, smoking hence appears to leave the strongest tracks in the genome.

"The good news is that the level of DNA methylation is not written in stone," Brenner said. "Unlike mutations in the DNA building units, it is reversible. That means, for example, that an unfavorable methylation status may change after smoking cessation and the mortality risk may drop again significantly."

Only ten positions in the genome make up an epigenetic risk profile

Of the 58 CpGs, the scientists selected those ten with the strongest correlation with mortality. This epigenetic risk profile alone enabled them to predict the so-called all-cause mortality (cancer, cardiovascular diseases, and others). Study participants whose genome exhibited an "unfavorable" methylation status at five or more of these sites had a risk of death within the 14-year observation period that was seven times that of study participants whose methylation at these positions showed no abnormalities.

The DNA methylation revealed a much stronger link to survival than all other previously studied alterations in individual DNA building blocks

(SNPs, single nucleotide polymorphisms). The epigenetic risk profile thus proved to be a more accurate indicator for lifespan than all other previously established genetic risk profiles that are based on alterations in DNA building blocks.

"We were surprised that the methylation status of only ten positions of our genome correlates so strongly with all-cause mortality," commented Brenner. "We found even stronger links to mortality from cardiovascular diseases. Now it is important to find out which prevention measures are most effective to achieve a beneficial impact on the methylation profile and mortality."

More information: Yan Zhang et al, DNA methylation signatures in peripheral blood strongly predict all-cause mortality, *Nature Communications* (2017). DOI: 10.1038/ncomms14617

* Gao, X., Jia, M., Zhang, Y., Breitling, L. P. & Brenner, H. DNA methylation changes of whole blood cells in response to active smoking exposure in adults: a systematic review of DNA methylation studies. Clin Epigenetics. 7, 113 (2015).

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