



Commentary

Epigenetic age acceleration as an effective predictor of diseases and mortality in the elderly

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ARTICLE INFO

Article History:

Received 23 November 2020

Accepted 2 December 2020

Available online xxx

As the nurture side to the nature of genetics, epigenetics offers a link between the genome and the environment. This is important for studying diseases and complex health traits, such as ageing and longevity, for which a broad range of environmental factors are involved. Considerable effort has been spent building health and ageing indexes based on environmental, behavioural and social variables, as well as biochemical markers, for classification and prediction purposes. The recent introduction of DNA methylation-based biological age estimator (DNAm age) [1] offers a promising approach to assess biological ageing and related conditions. In this issue of *EBioMedicine*, Wang et al. [2] reports a comparative analysis of the different versions of DNAm age providing useful information to guide their application in health practice and basic research.

Multiple epigenome-wide association studies on ageing have been performed and reported large numbers of age-dependant DNA methylation sites in the genome with significant impact on all-cause mortality. This is not surprising given the fact that ageing is a biological phenomenon that affects all functional systems, with epigenetic regulations involved in influencing or in response to the ageing process. Importantly, the global epigenetic remodelling offers an opportunity to define biomarkers of age and to measure individual's biological age as an indicator of general health.

Similar to the current ageing and health indexes that are built upon many social, environmental and clinical variables, the first-generation DNAm age estimators collapse multiple age-related methylation sites to define epigenetic metrics stably applicable across tissues and populations and then contrast with chronological age to obtain epigenetic age acceleration estimates. These include intrinsic and extrinsic epigenetic age accelerations (IEAA, EEAA) which are of more biological relevance as indicators of an individual's rate of biological ageing. The second-generation estimators have evolved to incorporate ageing-related traits to define composite epigenetic age metrics, e.g. DNAm

PhenoAgeAccel [3] and DNAm GrimAgeAccel [4] predictive of diseases in the elderly and risk of death. The work by Wang et al. [2] assessed performances of IEAA, EEAA, DNAm PhenoAgeAccel, DNAm GrimAgeAccel and DNAm-related mortality risk score (DNAmRS) by applying them to the same samples enabling empirical comparison based on two large independent cohorts: the Normative aging Study and the Cooperative Health Research in the Region of Augsburg cohort. Their results show that the second generation of DNAm ages incorporating additional ageing-related markers outperform the first-generation estimators. Although the finding that GrimAgeAccel and DNAmRS are strong predictors of all-cause death could reflect the fact that both were derived with mortality as the primary endpoint, the improved performance of second-generation estimators shows the powerful enrichment of the composite approach. This is encouraging because important markers of ageing and diseases can be included in the estimators, offering plenty of opportunities for extension and broad applications. In the field of ageing and longevity research, the apolipoprotein E gene has been the most replicated gene associated with human longevity and Alzheimer's dementia [5]. It is thus highly expected that integration of apolipoprotein E genotypes in the second-generation estimators should further improve their predictive power for ageing-related conditions across populations.

As current DNAm age algorithms are primarily proposed to correlate with chronological age and/or all-cause mortality, their immediate implication lies in ageing research and health care of the elderly. In fact, many studies on ageing have been performed associating DNAm age and acceleration with ageing phenotypes (cognitive function, physical ability, etc.) and ageing-related diseases. As a result of rapid global population ageing, especially in the developed countries, healthcare of the elderly is becoming a critical public health challenge. Identifying vulnerable older people is a critical and essential first step in the development of individualised healthcare strategies to promote healthy ageing and extend healthspan. In this regard, the epigenetic age estimator can serve as operational instruments for classification of the old people for risk assessment by the healthcare providers.

The poor performance on cancer risk prediction as reported in Wang et al. [2] emphasises the limitation of current DNAm age metrics in clinical applications, although the predictive value of GrimAgeAccel for myocardial infarction and stroke may suggest potential utility in clinical practice. Nevertheless, the modelling algorithm of GrimAgeAccel can be modified to correlate and to

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predict disease-specific conditions and endpoints such as risks of cancer recurrence, metastasis, and time to recurrence/metastasis, and clinical prognosis, etc. Of course, the development of clinical prognostic models requires stringent evaluation of predictive performances such as sensitivity, specificity and overall accuracy. Although there are challenges, such applications can be highly valuable for designing optimal treatment and management strategies in clinical practice.

The composite feature empowers second-generation epigenetic age acceleration metrics as valuable tools for basic research in ageing and geriatrics and as potential practical instruments for healthcare and clinical applications. Current application of the estimators is still based on data measured by genome-wide methylation arrays from ageing research. Development of validated stand-alone test sets applicable to different populations should help with facilitating broad and economic operational implementation in public health and clinical applications.

Declaration of Interests

The author has no conflicts of interest to disclose.

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