Clinical application of facial aging clocks

Yiyang Wang,[a,b,c] Kehang Mao,[a,c] Haotian Zhai,[a,c] and Jing-Dong Jackie Han[a,*]

[a]Peking-Tsinghua Center for Life Sciences, Academy for Advanced Interdisciplinary Studies, Center for Quantitative Biology (CQB), Peking University, Beijing, 100871, China
[b]Key Laboratory of Computational Biology, Shanghai Institute of Nutrition and Health, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Shanghai, China

The Lancet Regional Health - Western Pacific 2023;37: 100858

Published Online xxx https://doi.org/10.1016/j.lanwpc.2023.100858

Aging process potentially drives numerous diseases development[1] and manifests great heterogeneity among individuals. Thus, monitoring and quantifying aging rate is a fundamental question. Scientists have constructed a variety of aging clocks by machine learning to predict chronological age. The residue between prediction and chronological age followed by regressing out age effects is taken as the biological aging rate. DNA methylation clocks[2] are the mostly widely recognized aging clocks. However, bio-sample collection and high-throughput sequencing are often invasive, time-consuming and expensive, which may hinder the translational application of aging clocks. What's more, the relatively small sample size of omics-based aging clocks may affect the model generalization and limits the application of powerful deep learning methods.

To tackle the above problems, we have built facial aging clocks by support vector regression (SVR)[3] and deep convolutional neuron networks (CNN)[4] with MAD as 6.0 and 2.8 years respectively. Aging rate derived from facial aging clock shows significant correlation with transcriptome and identifies molecular mediators of lifestyles.[4] These indicate that facial aging clock can accurately capture the biological age and detect associated molecular patterns. In addition, facial aging clock trained on perceived age creatively avoids the dilemma of taking model error as the true aging rate. Age based on only face appearance estimated by human judges are defined as perceived age and have been shown to be a biological age of the face. As perceived age trained facial aging clocks are actually trained on biological age instead of age, it is not surprising that such a clock is more associated with health indicators than chronological age train models. Such a clock can also reflect how humans judge other people's age.

Studies have shown that numerous diseases associate with aging rate. DNA methylation aging clock acceleration is observed in diseases like tumors,[5] combat PTSD,[6] and even can reflect mortality risk.[7] Facial aging clock acceleration is also observed for systemic inflammation, high blood cholesterol and uric acid.[3,4] Convenient data acquisition and processing, and high accuracy confer promising translational potential of facial aging clocks. Single cell RNA-seq clock can be accelerated by 10–20 years in CoVID and lupus, and decelerated by decades in super centenarians.[8] Unlike other omics aging clocks, facial aging clock is suitable to clinical scenarios. Facial images taking and biological age prediction takes only several minutes, thus well fit to daily monitoring of aging rate. Except common clinical evaluation markers of diseases, aging rate dynamics of patients as a novel biomarker can provide doctors evaluation of quantitative patients aging status and objective evaluation of therapies. As aging acceleration often reflects disease risk and progression, facial aging clock application may help doctors to optimize drugs and therapies, thus a better prognosis. Accelerated aging may indicate future risk of some diseases, can thus guide people to alter their lifestyles. Another application scenario may be for clinicians to monitor patients health management and relieving clinicians from overloaded routine monitoring. Overall, we envision the non-Invasive and low-cost facial aging clock and even disease risk assessment to be affordable and practical applications under many clinical scenarios, as the workflow shown in Fig. 1.

Furthermore, application of facial aging clocks is not restricted to only hospitals. Facial aging clock can be utilized for evaluating daily anti-aging interventions like calorie restriction, metformin and personalized therapies. If this clock is integrated to smart phones in the soon future, daily monitoring of aging is available to all people under any situations. We believe that facial aging clock will prompt people to get accustomed to monitoring aging for optimum health. From the public health perspective, monitoring aging by facial aging clocks can prevent or suspend diseases progression, and ease the economical and clinical pressure.

Additionally, some diseases seem to be linked with face morphology. Various diseases may be manifested through alterations in facial features, such as in the case of Down syndrome.[9] Facial appearance has been used as a diagnostic tool to facilitate early detection. Deep learning-based analysis of facial images has shown high accuracy in genetic disorders.[10] This implicates that pre-diagnosis and risk assessment of certain diseases are clinically practical based on facial images. With the advance in artificial intelligence and cohort data accumulation, we expect that a plethora of facial models will

*Corresponding author.
E-mail address: jackie.han@pku.edu.cn (J.-D. Jackie Han).

[c]These authors contributed equally.

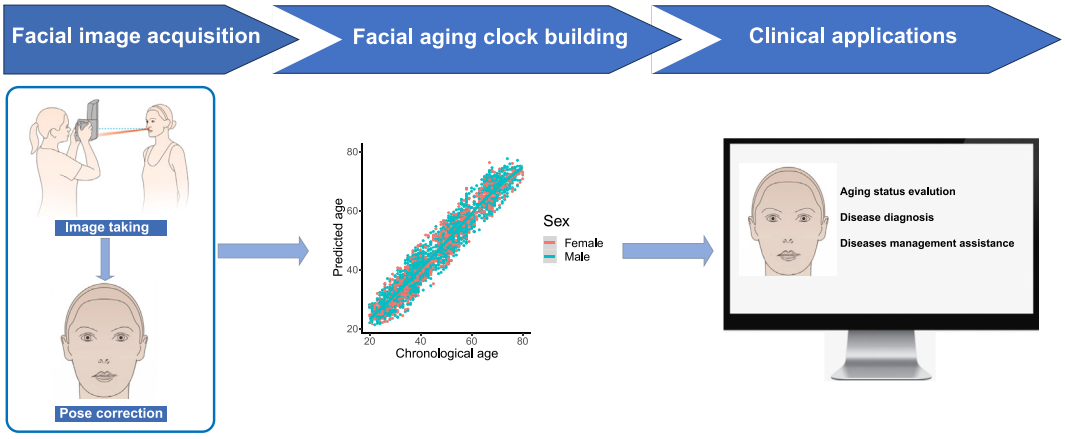

Fig. 1: Workflow of building and applying facial aging clocks.

emerge and assist doctors to prevent, diagnose and manage aging and diseases in the near future.

However, there exist some limitations on clinical application of facial aging clocks. The effect of geographical differences on faces may introduce confounding factors. Facial appearance exhibits notable variations across different regions worldwide. Recent study of 3D facial images has further revealed significant disparities in facial morphology between East Asian and European populations.[11] Environmental and lifestyle factors also influence facial development.[12] Moreover, while deep learning-based facial image analysis holds promise for future clinical applications, it is important to acknowledge that facial changes associated with certain diseases can be subtle and may overlap with normal variations or non-disease-related factors. Finally, many diseases exhibit diverse manifestations. To enhance the accuracy and reliability of disease identification, it is crucial to adopt a comprehensive approach that integrates multiple diagnostic factors, including medical history, physical examinations and medical tests.

Contributors

J.D.J.H conceived and designed the comment. Y.W., K.M., H.Z. and J.D.J.H. wrote the manuscript.

Declaration of interests

The authors declare no competing interests.

Acknowledgements

This work was supported by grants from National Natural Science Foundation of China (NSFC) (Nos. 92049302 and 32088101), China Ministry of Science and Technology (No. 2020YFA0804000), to J.D.J.H.

References

1 Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. *Cell*. 2013;153(6):1194–1217.
2 Horvath S. DNA methylation age of human tissues and cell types. *Genome Biol*. 2013;14(10):R115.
3 Chen WY, Qian W, Wu G, et al. Three-dimensional human facial morphologies as robust aging markers. *Cell Res*. 2015;25(5):574–587.
4 Xia X, Chen XW, Wu G, et al. Three-dimensional facial-image analysis to predict heterogeneity of the human ageing rate and the impact of lifestyle. *Nat Metab*. 2020;2(9):946–957.
5 Kling T, Wenger A, Caren H. DNA methylation-based age estimation in pediatric healthy tissues and brain tumors. *Aging*. 2020;12(21):21037–21056.
6 Yang RT, Wu GWY, Verhoeven JE, et al. A DNA methylation clock associated with age-related illnesses and mortality is accelerated in men with combat PTSD (vol 52, pg 541, 2020). *Mol Psychiatry*. 2021;26(9):5010.
7 Zheng YN, Joyce BT, Colicino E, et al. Blood epigenetic age may predict cancer incidence and mortality. *eBioMedicine*. 2016;5:68–73.
8 Zhu H, Chen J, Liu K, et al. Human PBMC scRNA-seq–based aging clocks reveal ribosome to inflammation balance as a single-cell aging hallmark and super longevity. *Sci Adv*. 2023;9(26):eabq7599.
9 Kruszka P, Porras AR, Sobering AK, et al. Down syndrome in diverse populations. *Am J Med Genet*. 2017;173(1):42–53.
10 Gurovich Y, Hanani Y, Bar O, et al. Identifying facial phenotypes of genetic disorders using deep learning. *Nat Med*. 2019;25(1):60–64.
11 Zhang M, Wu S, Du S, et al. Genetic variants underlying differences in facial morphology in East Asian and European populations. *Nat Genet*. 2022;54(4):403–411.
12 Richmond S, Howe LJ, Lewis S, Stergiakouli E, Zhurov A. Facial genetics: a brief overview. *Front Genet*. 2018;9:462.