Figures and figure supplements

A whole lifespan mouse multi-tissue DNA methylation clock

Margarita V Meer et al
Figure 1. Construction of the WLMT clock. (A) Datasets used for the clock construction and initial validation. Radii of pie charts correspond to the number of samples in a group. The range of ages is shown above (in months). Performance of the whole-lifespan multi-tissue clock on training (B) and test (C) sets. MAE on training and test sets was 28.6 and 72.7 days, respectively. Tissues used are indicated on the right according to the color scheme. DOI: https://doi.org/10.7554/eLife.40675.003
Figure 1—figure supplement 1. Density plot for the number of CpG sites covered in all samples (A) and in samples with covered $2 \div 7 \cdot 10^6$ sites, which were used to train the WLMT clock (B).

DOI: https://doi.org/10.7554/eLife.40675.004
Figure 1—figure supplement 2. Principle component analysis of samples sequenced in the study. Library 'M20' was not used in the preparation of the clock.
DOI: https://doi.org/10.7554/eLife.40675.005
Figure 1—figure supplement 3. Performance of the WLMT clock on male (blue) and female (pink) samples. DOI: https://doi.org/10.7554/eLife.40675.006
Figure 1—figure supplement 4. Number of reads obtained for the sequenced samples.
DOI: https://doi.org/10.7554/eLife.40675.007
Figure 2. Overlap in CpG sites among mouse DNA methylation clocks. (A) overlap in CpG sites. (B) overlap in genes containing the clock sites. * - significant with \( p < 10^{-4}\) (two-tailed Chi-square test with Yates correction).
DOI: https://doi.org/10.7554/eLife.40675.008
Figure 2—figure supplement 1. Distribution of WLMT clock CpG sites along the mouse genome. Sites with positive weights (increasing methylation with age) are shown in green, and those with negative weights (decreasing methylation with age) in red.
DOI: https://doi.org/10.7554/eLife.40675.009
Figure 2—figure supplement 2. Location of CpG sites forming the four epigenetic clocks in the mouse genome: WLMT sites are shown in blue, YOMT sites in green, blood clock sites in red and liver clock sites in orange. DOI: https://doi.org/10.7554/eLife.40675.010
Figure 2—figure supplement 3. Frequency of the occurrence of WLMT clock sites in 100 clocks generated based on the robustness study. 100 clocks are trained on different subsets of the set of samples used in WLMT construction. (A) Density plot showing the overall distribution of frequencies of WLMT clock sites as found in the generated 100 clocks. Carpet plot shows the exact values of frequencies. (B) Relation of the absolute values of weight of sites in the WLMT clock and frequency of these sites in the 100 alternative clocks.

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Figure 2—figure supplement 4. Age-related changes in DNA methylation of the ten WLMT clock sites with highest positive weights. Tissues used in construction of the clock are shown.
DOI: https://doi.org/10.7554/eLife.40675.012
Figure 2—figure supplement 5. Age-related changes in DNA methylation for the ten WLMT clock sites with lowest negative weights.
DOI: https://doi.org/10.7554/eLife.40675.013
Figure 2—figure supplement 6. Density plots showing distribution of weights of CpG clock sites in the four mouse clocks.
DOI: https://doi.org/10.7554/eLife.40675.014
Figure 3. Absolute errors of four mouse DNA methylation clocks applied to untreated wild-type samples. (A) In this case, WLMT clock was applied to its test set, whereas for the other age predictors this set also included their training set samples. (B) Blood samples which were not used in any of the clocks. (C) Only liver samples. (D) Samples of all tissues, excluding those used in the YOMT clock. (E) Samples of all non-blood tissues. (F) All tissues, excluding liver.

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Figure 3—figure supplement 1. Performance of the WLMT, blood, YOMT and liver clocks on the liver samples not included into the WLMT and liver training sets. ΔAge shows difference between DNAm age and chronological age. Chronological age of the included samples is 180 days. MAE is 244 days for the WLMT and 65 days for the liver clock.

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Figure 3—figure supplement 2. Performance of the WLMT, blood, YOMT and liver clocks. WLMT: only test samples are included. YOMT: test and training sets are shown. Blood samples have not been used in development of this clock. Blood clock: all blood samples belong to the training set, while all other tissues to the test set. Liver clock: only test samples are shown. DOI: https://doi.org/10.7554/eLife.40675.017
Figure 4. DNA methylation (DNAm) ages estimated for an independent dataset. An additional dataset (Reizel et al., 2018) was tested with the four clocks. Solid line represents a perfect correspondence between DNAm age and chronological age. Dashed lines show slopes of linear regressions made for each DNAm clock based on the age values estimated with it. Slopes: 0.14 (YOMT), 0.16 (liver), 1.24 (WLMT), 0.45 (blood). p-values: $p = 1.4 \cdot 10^{-39}$ (YOMT), $p = 2.8 \cdot 10^{-29}$ (liver), $p = 0.12$ (WLMT), $p = 6.4 \cdot 10^{-4}$ (blood).

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Figure 5. Difference in DNAm age estimated by four age predictors and chronological age based on WLMT, blood, YOMT and liver clocks. Untreated and wild-type samples are shown in green, and intervention samples in orange. (A) Effect of caloric restriction in mouse strain C57BL/6, DNA from blood. (B) Effect of caloric restriction, mouse strain B6D2F1, DNA from blood. (C) Conversion of fibroblasts to iPSCs, DNA from cultured cells. (D) Growth hormone receptor knockout, DNA from blood. (E) Snell dwarf mice, DNA from blood. (F) Ames dwarf mice, DNA from liver. ΔAge was defined as the difference between the DNAm age and the chronological age. * p < 5 · 10⁻², ** p < 1 · 10⁻², *** p < 10⁻³.

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