Next Generation Aging Clock: A Novel Approach to Decoding Human Aging Through Over 3000 Cellular Pathways

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Abstract:

The paper introduces a novel method, termed as 'Next Generation Aging Clock Models', which enhance disease prediction capabilities by defining aging clocks for each cellular component or pathway, as opposed to traditional aging clocks that provide a single value for the whole human body. The method is implemented in two stages: first, the pre-training stage that generates 3028 generic pathway aging models by integrating age-related genome-wide DNA methylation data with gene ontology and signaling pathway; second, the fine-tuning stage that produces 30280 disease-specific pathway aging models using DNA methylation profiling from 3263 samples across 10 age-related diseases. The Next Generation Aging Clock Models have demonstrated exceptional performance in predicting diseases. For example, the aging index of blood vessel endothelial cell migration can predict Atherosclerosis with an odds ratio of 80. Alzheimer's disease can be predicted by the aging index of response to DNA damage stimulus, with an odds ratio of 3.1. Major Depressive Disorder can be predicted by the organization of the mitochondrion, with an odds ratio of 4.4. Breast cancer can be predicted by DNA repair, with an odds ratio of 3.4, and the severity of COVID-19 can be predicted by neutrophil degranulation, with an odds ratio of 8.5. Furthermore, the models have allowed the categorization of diseases into nucleus aging and cytoplasm aging types. The former includes Alzheimer's disease, Mild Cognitive Impairment, breast cancer, colon cancer, and osteoporosis. The latter includes Parkinson's disease, depression, atherosclerosis, rheumatoid arthritis, and COVID-19 severity. This innovative approach is expected to be a valuable tool for research into aging-related diseases and for personalized aging interventions.

Keywords: Next Generation Aging Clock Models; Aging Clocks; Hallmarks of Aging; Capomics

Introduction

The concept of biological age, distinct from chronological age, has become significant in aging research. This emphasizes the importance of aging biomarkers in studying age-related diseases and implementing longevity interventions [1]. Among the various models of biological aging, the DNA methylation clock is the most studied. This model predicts age based on the methylation status of specific CpG sites in the genome [2]. The discrepancy between predicted age and chronological age, referred to as 'age acceleration', is employed

to explore disease correlations and predict health outcomes [3]. The first type of clock fits chronological age such as Horvath clock [4] and Hannum clock[5]. The second type of clocks estimate mortality risk such as GrimAge clock [6] and PhenoAge clock [7]. The third type of clock analyzes longitudinal data, such as DunedinPoAm [8] and Pace of Aging [9].

The traditional aging clock, which provides a single value for the entire human body and predicts disease and mortality risk, has limited organ-specific disease prediction capabilities. Recently, an organ-specific clock that provides aging measures for ten organs has been introduced [10]. This multi-dimensional aging clock can forecast diseases specific to certain organs. For example, it has shown that accelerated heart aging boosts the risk of heart failure by 250%. Additionally, fast-paced brain and vascular aging can predict the progression of Alzheimer's disease. A recent paper disclosed that the biological age of one organ could selectively impact the aging of other organ systems, thereby revealing a multiorgan aging network [11].

Systems biology views the human body as a multi-level complex network, spanning from genes and cells to organs and systems. Given this, the basic biological process of aging leaves traces and records at each of these levels. With this in mind, we suggest expanding the concept of the biological aging clock to introduce the Pathway Aging Model. This model establishes an independent clock for each pathway, allowing for individualized assessment of aging status in each pathway. Given the thousands of pathways, we suggest that these advanced dimensional aging clocks could offer a more profound, detailed insight into aging and its relation to various illnesses. For complex conditions like neuropsychiatric diseases that impact multiple organs, the pathway clock could be especially beneficial. It can aid in understanding disease variation, facilitating disease subtyping and classification, and guiding personalized prevention and treatment strategies.

Methods

Generic Pathway Aging Models

As depicted in Fig.1, we downloaded pathway definitions from The Molecular Signatures Database (MSigDB) (http://www.gsea-msigdb.org/gsea/msigdb/index.jsp). These include gene set definitions from various sources such as Gene Ontology (GO), KEGG pathway, REACTOME pathways, Pathway Interaction Database (PID), WikiPathways (WP), BIOCARTA pathways, and the Hallmark gene set. Notably, Gene Ontology is further divided into three functional categories: Biological Process (GOBP), Molecular Function (GOMF), and Cellular Component (GOCC). For clarity, we use the term "pathway" to refer to the cellular functions performed by all these Gene sets.

We divide all genes within the pathway into signature genes positively associated with aging (Pos-genes), and signature genes negatively associated with aging (Neg-genes). Specifically, we first obtained genome-wide DNA methylation data from GEO data GSE40279. This is the Illumina Infinium 450k Human DNA methylation Beadchip on whole blood samples of 656 individuals[5]. We compute the average value of methylation sites in each gene's promoter

region as its methylation feature value. Subsequently, we determine the correlation between each gene's methylation feature value and the chronological age of the subjects.

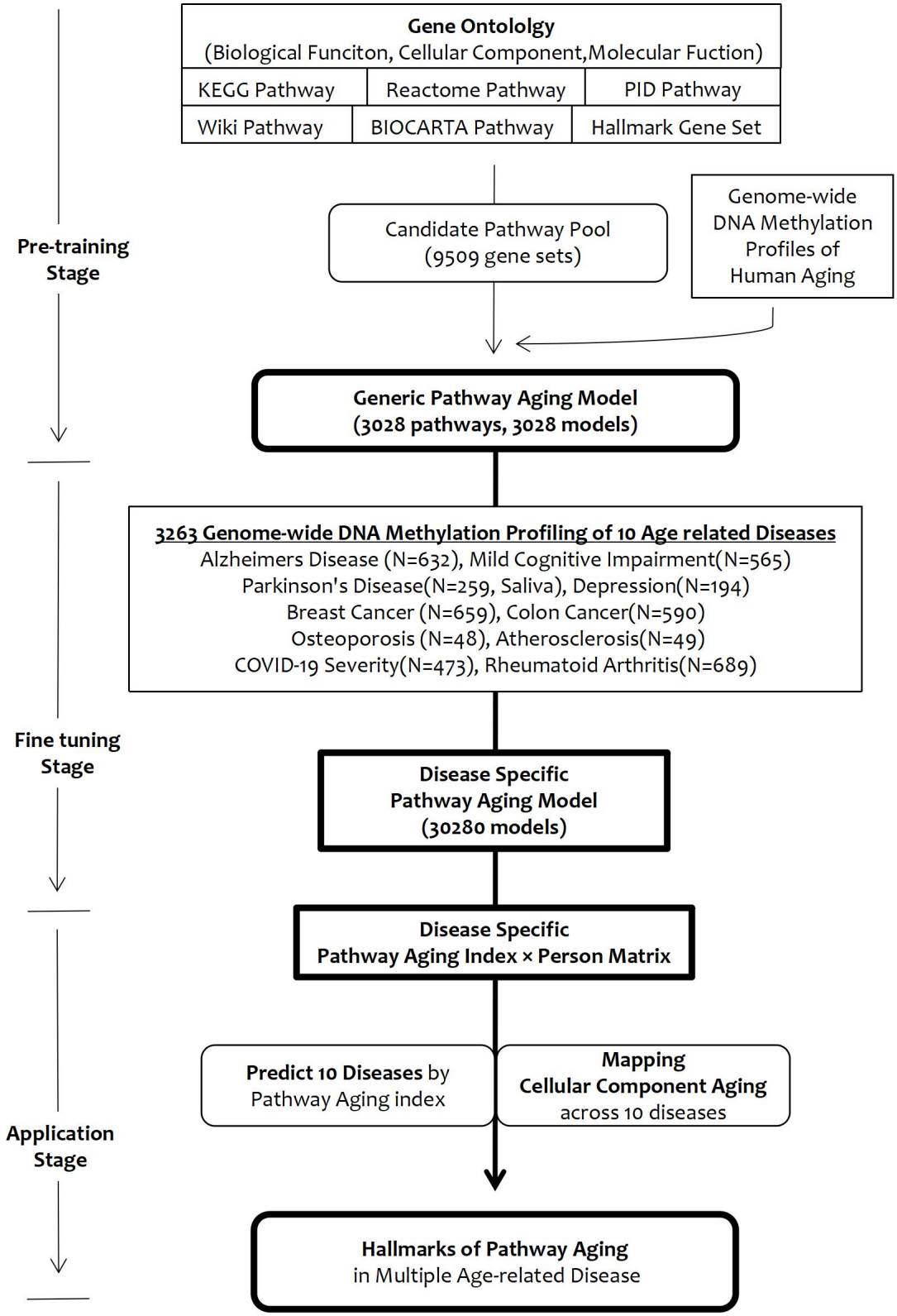


Figure 1 The Framework of the Pathway Aging Model.

Within each pathway, genes that are significantly positively correlated with age are classified as Pos-genes, while those significantly negatively correlated with age are classified as

Neg-genes. Theoretically, the aging of each pathway can be indicated by the statistical difference between the DNA methylation values of Pos-genes and Neg-genes. Specifically, a T-test is conducted between the DNA methylation values of Pos-genes and Neg-genes for each DNA methylation profile. The resulting T-statistics are used as the pathway aging index (PA index).

Disease Specific Pathway Aging Models

We interrogated 10 age-related diseases using genome-wide DNA methylation profiling of clinical cohorts. The data was downloaded from the GEO database. Unless specified otherwise, these data are derived from whole blood samples, using the Illumina 450k/850k microarray platform. The total number of clinical samples is 3263. The data examined in this study encompasses several conditions, including Alzheimer's Disease [12] (GSE153712, N=632), Mild Cognitive Impairment [12] (GSE153712, N=565), Parkinson's Disease [13] (GSE111223, N=259, Saliva), Osteoporosis [14](GSE99624, N=48), Breast Cancer (GSE51032, N=659), Colon Cancer (GSE51032, N=590), Atherosclerosis [15] (GSE46394, N=49), Depression [16](GSE113725, N=194) , COVID-19 Severity [17](GSE179325, N=473) , and Rheumatoid Arthritis [18] (N=689) .

Most of the clinical data provided includes both a disease group and a healthy control group, with the exception of the COVID-19 severity data. This particular dataset includes 473 COVID-19 positive individuals. Patients are classified based on the WHO clinical ordinal scale: the mild group (PCR positive individuals, either ambulatory or hospitalized with mild symptoms, on scales 1-4), and the severe group (PCR positive individuals, hospitalized with severe symptoms or who have died, on scales 5-8). The aim of this analysis is to determine whether the pathway aging index can predict the severity of a patient's condition, specifically predicting if it will be severe or mild.

The data for breast cancer and colon cancer comes from prospective research involving 845 participants. They were analyzed using a 450k methylation microarray (GSE51032). According to the dataset description on the GEO website, at the time of the last follow-up, 424 participants remained cancer-free. Out of the remaining participants, 235 developed primary breast cancer and 166 developed primary colorectal cancer. Therefore, in the breast cancer dataset, the class label differentiates between the disease group (235) and the control group (424). Similarly, in the colon cancer dataset, the class label differentiates between the disease group (166) and the control group (424).

For each disease dataset, we calculate and obtain a set of genes significantly related to the disease phenotype. More specifically, the average value of all methylation sites in each gene promoter region serves as the gene's methylation value. We use the t-test to calculate the significance of the difference between each gene's methylation value in the disease group versus the control group. The significantly different genes serve as the disease-related gene set.

For a specific pathway, the aforementioned Pos-genes, i.e., genes positively correlated with age, calculate the intersection with the current disease positively correlated gene set to form disease specific Pos-genes, abbreviated as dsPos-genes. Similarly, genes negatively correlated

with age in the pathway, i.e., Neg-genes, calculate the intersection with the current disease negatively correlated gene set to form disease specific Neg-genes, abbreviated as dsNeg-genes.

For each DNA methylation data, we calculate the pathway aging index. The aging of each pathway can be indicated by the statistical difference between the DNA methylation values of disease-specific Pos-genes and disease-specific Neg-genes. Specifically, a T-test is conducted between the DNA methylation values of dsPos-genes and dsNeg-genes for each DNA methylation profile. The resulting T-statistics are used as the pathway aging index (PA index). For the sake of demonstration, the PA index is rescaled to a range between 0 and 1.

Using Pathway Aging Index to Predict Disease

After the above calculations, the methylation dataset of each disease is transformed from gene×samples to Pa-index × samples matrix. For each pathway, we use the T-test to determine the difference in the pathway aging index between the disease group and the control group. We then calculate the T-test's p-value and use the odds ratio to assess each pathway index's predictive power for the disease.

For each pathway, we use the T-test to determine the difference in the pathway aging index between the disease group and the control group. We calculate the T-test's p-value and use the odds ratio to assess each pathway index's predictive power for the disease. The calculation process for the odds ratio is as follows: We calculate the average pathway aging index across all samples in the current dataset. Samples with values higher than the average are classified as the PA-High group, and those with lower values are classified as the PA-Low group. Finally, we use the Fisher exact test to determine the difference in disease probability between the PA-High and PA-Low groups, and we obtain the odds ratio value.

Global Analysis of Pathway Aging Index with Multiple Age-Related Diseases

For each pathway, we calculated the sum of their odds ratios for predicting all 10 diseases. This sum formed an index, known as the OA score (Overall age relativeness score), which measures the correlation between a certain pathway and all age-related diseases. Thus, each pathway has an OA score. We ranked all pathways in descending order according to their OA scores. We then selected the top 30 pathways and created a heatmap of their correlations (odds ratios) with the 10 diseases, which can be seen in Fig.4A. Note, the number on each square in the figure represents the normalized odds ratio.

For the top 30 pathways, known for their strong predictive ability for age-related diseases, we calculated the correlation between pathways using the Pearson correlation coefficient. This calculation resulted in the heatmap shown in Fig.4B.

The results in Fig.4B divide all pathways into two categories. Most pathways have a strong positive correlation, as indicated by the yellow block in the figure. A few pathways show a negative correlation with other pathways, as represented by the rose color. Thus we selected

three representative pathways from each type as indicators. Using the correlation (odds ratio) of these six pathways with each disease, we created a clustering diagram, shown in Fig.5A.

Results

The Framework of the Pathway Aging Model

The entire computational framework, as shown in Figure 1, consists of three stages: pre-training, fine-tuning, and application.

In the pre-training stage, we aim to quantify the aging of all biological processes or structures theoretically, so we initially collected various gene sets reflecting biological functions. Gene ontology is a crucial source that defines the biological process, molecular function, and cellular component. In addition, numerous databases exist about the signaling pathway, such as the reactome pathway. This resulted in 9509 candidate gene set definitions. For simplicity, we refer to all these gene sets as pathways. Ideally, we will define and calculate aging indexes for all gene sets.

We filtered the previously mentioned pathways, retaining only those with an intersection of age-associated gene sets of 30 genes or more. This process retained 3,028 pathways, including 1,295 Gene Ontology Biological Process (GOBP), 192 Gene Ontology Molecular Function (GOMF), 175 Gene Ontology Cellular Component (GOCC), and 184 Reactome signaling pathways, among others.

Each biological process or subcellular structure has genes that increase or decrease with aging. In relation to DNA methylation data, this usually means that the methylation of some gene promoter regions increases, while others decrease. Consequently, we used a whole genome DNA methylation dataset with age information to calculate the correlation between each gene and age. This resulted in age positively correlated genes, referred to as pos genes, and negatively correlated genes, known as neg genes.

Our basic assumption is that as aging occurs, the degree of difference between positive and negative genes in a biological process or structure increases. Therefore, we use a T-test to statistically measure the significant difference in methylation degree between the positive and negative gene groups. The larger the absolute value of the t-score, the higher the degree of aging. Hence, we use the t-score derived from the T-test to quantify the degree of aging of a pathway. Consequently, for each pathway, the pathway aging index equals this t-score.

In the fine-tuning stage, we adjust the pos and neg gene of each of the above pathways. We have integrated genome-wide DNA methylation profiling from 3263 samples across 10 age-related diseases. For each disease, we first identified a list of genes significantly related to the disease at the gene level. For each pathway, its pos and neg genes include genes that are not related to the current disease. Hence, we intersect the pos gene with the list of genes related to the current disease to get the disease-specific pos gene, dsPos-genes, and similarly, we get the disease-specific neg genes, dsNeg-genes.

For each of the 3028 pathways, we combine it with 10 diseases to generate 10 disease-specific models. Therefore, in total, we generate 30280 disease-specific pathway aging models.

In the application stage, we use the specific model formed by the combination of the above pathway and disease to transform the methylation profile of each disease into a new matrix, the PA-index×samples matrix, where each row is a pathway aging index. We use these matrices to explore pathways that can predict diseases and examine the common characteristics of various diseases in terms of the aging degree of pathways.

Pathway Aging as Predictive Factors of Disease

Figures 2 and 3 illustrate the relationship between various diseases and the pathway aging index. As an example, Figure 2A exhibits the pathway associated with Atherosclerosis, a specific disease. The initial pathway presents the results of GO blood vessel endothelial cell migration (GOBP). The orange box plot indicates a significant difference between the disease and the control groups.

The figure's lower section includes the odds ratio (OR) and the p-value. The method to calculate the odds ratio is provided in the methods section. Briefly, it involves dividing a certain aging index into high and low groups based on its mean value. Then, it measures how frequently the disease appears in the high group compared to the low group. If the OR is greater than 1, the larger the value, the higher the likelihood of this variable becoming a risk factor for the disease, and the stronger its predictive power.

The p-value signifies the significance of the difference between the disease and control groups' aging index. It is obtained using a t-test. As the figure suggests, this pathway aging index can predict Atherosclerosis with an odds ratio of 80 and a p-value of 9.5e-15. Another variable with strong predictive power is GO artery development.

Endothelial cells in blood vessels play a significant regulatory role in Atherosclerosis, undergoing epigenetic reprogramming throughout the disease process [19]. Our findings suggest that a whole blood DNA methylation analysis can capture this crucial variable in Atherosclerosis progression. Additionally, an increase in the aging degree of the biological process of blood vessel endothelial cell migration raises the risk of Atherosclerosis.

The blue box plot in Fig.2a demonstrates the correlation between the aging index of the blood vessel endothelial cell migration pathway and age in a naturally healthy population. The data used is the GEO data GSE40279, mentioned in the methods section. This data is sourced from The Illumina Infinium 450k Human DNA methylation Beadchip, which includes whole blood samples from 656 individuals. We use the age of 40 as a cutoff to split the population into older and younger groups, comparing the significant difference between the aging index of the blood vessel endothelial cell migration pathway in both groups. The p-value of the t-test is 3.8e-13. The interpretation of all orange and blue box plots in Fig.2 and Fig.3 is consistent with this case.

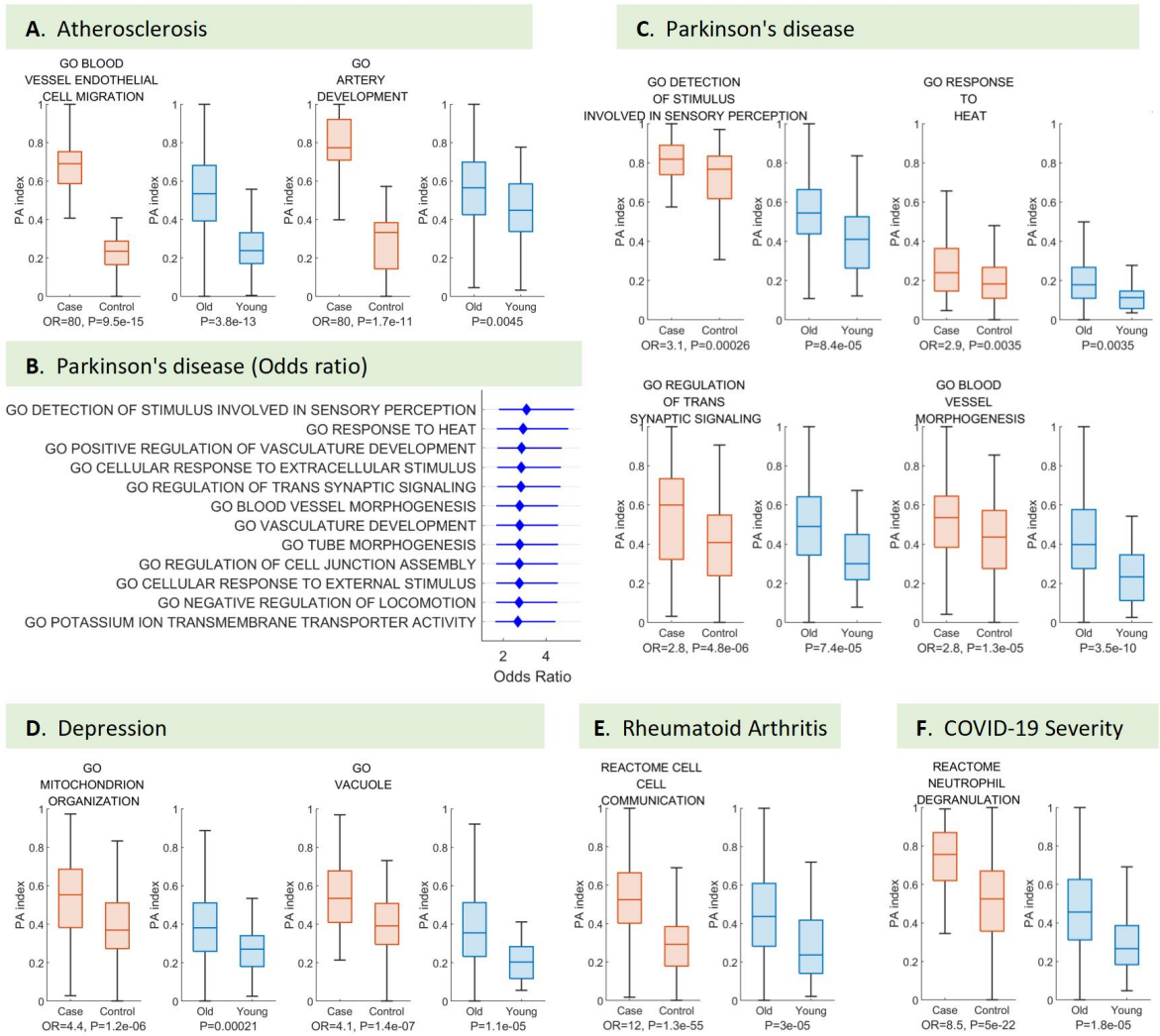


Figure 2 Pathway Aging as Predictive Factors of Disease. Subplots A-F depict the representative pathway that can predict various diseases. A. Atherosclerosis. B and C. Parkinson's disease. D. Major depressive disorders. E. Rheumatoid arthritis. F. COVID-19 severity.

In our analysis of Parkinson's disease, we identified pathways with the highest odds ratio (fig. 2B and Fig.2C) primarily associated with the response to environmental stimuli. This includes the detection of stimulus involved in sensory perception (OR=3.1), response to heat (OR=2.9), and biological processes like neural, vascular remodeling such as regulation of trans synaptic signaling (OR=2.8), and blood vessel morphogenesis (OR=2.8).

Pathways related to cellular components were also prominent. For example, in major depressive disorders, the aging index of mitochondrion organization (OR = 4.4) and vacuole (OR = 4.1) can predict these disorders (Fig.2D). Major Depressive Disorder (MDD) affects the central nervous system and physiological performance. New understanding of MDD links symptoms like fatigue and lack of motivation to reduced mitochondrial ATP production and

changes in the mitochondrial network, suggesting potential biomarkers for MDD diagnosis and treatment [20].

The Reactome pathway also contributes to predictive pathway definitions. For instance, cell-cell communication from Reactome can predict Rheumatoid Arthritis with an odds ratio (OR) of 12. Similarly, Reactome's neutrophil degranulation can predict COVID-19 severity with an OR of 8.5.

The correlation between other diseases and the pathway aging index is illustrated in Figure 3. Notably, Alzheimer's disease, a neurodegenerative disease, and breast cancer show similar DNA damage repair-related pathway aging features. For instance, Alzheimer's disease could be predicted by the aging index of GO cellular response to DNA damage stimulus (OR=3.1) and GO DNA repair (OR=3.0), and breast cancer by the Hallmark gene set: DNA repair (OR=3.4).

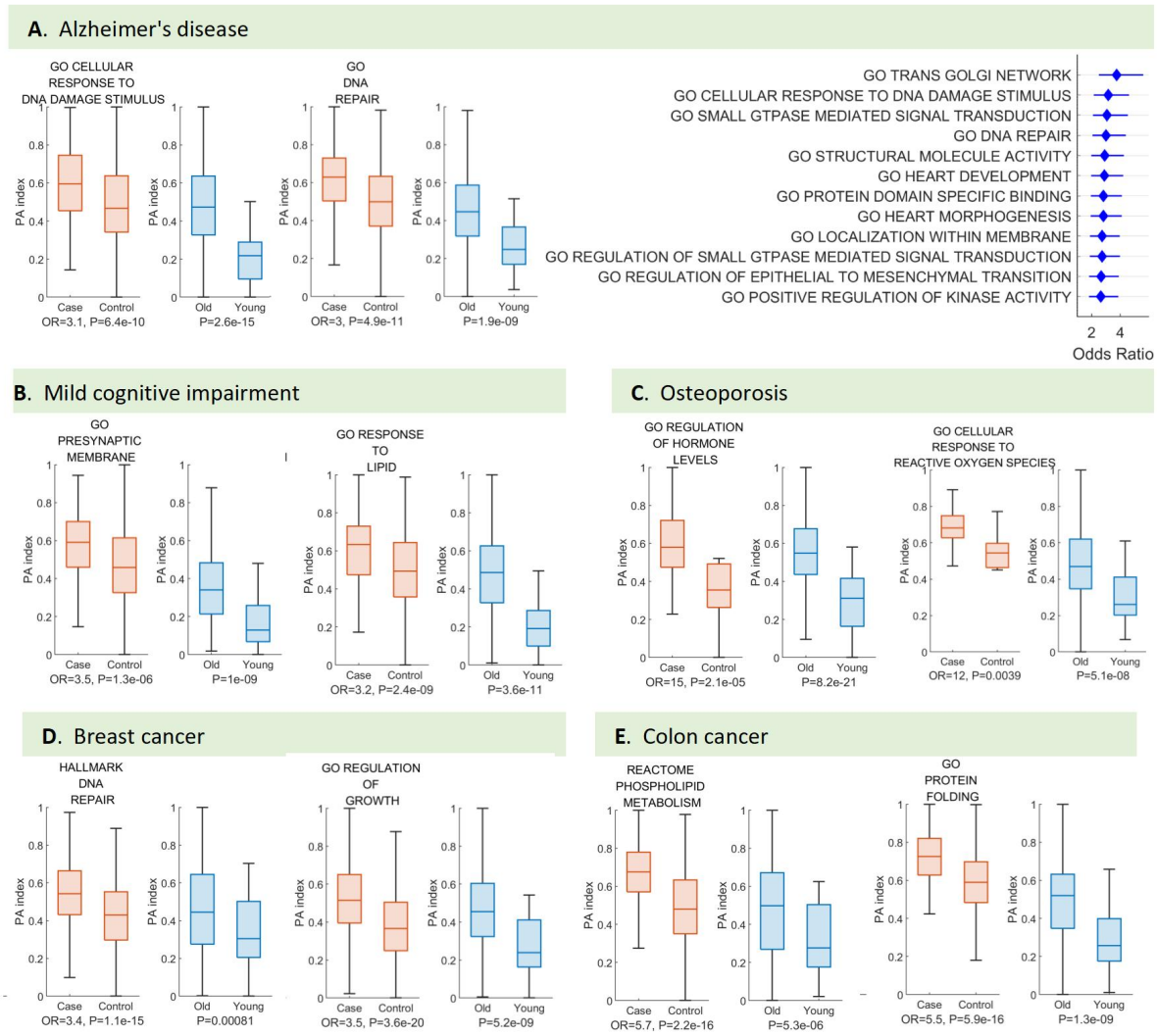


Figure 3 Pathway Aging as Predictive Factors of Disease (cont.). Subplots A-E depict the representative pathways that can predict various diseases. A. Alzheimer's Disease. B. Mild Cognitive Impairment. C. Osteoporosis. D. Breast Cancer. E. Colon Cancer.

These findings suggest that DNA methylation detection in whole blood can generally reflect pathway aging, which is closely associated with the pathogenesis of various diseases. However, an exception was found with Parkinson's disease, where saliva samples were used, implying that saliva, like whole blood, could also be a valuable source of information for reflecting pathway aging.

The Organelle Aging Index is Linked to Multiple Age-Related Diseases

The study of organ aging offers valuable insights into aging research and holds significant potential for personalized disease intervention. We subsequently pose the question: can aging be quantified at the level of cellular components, organelles, or even protein complexes?

We used the odds ratio of the pathway aging index's disease prediction ability as our calculation unit to construct a global analysis diagram. This diagram illustrates the correlation between the cellular component pathway index and ten types of age-related diseases. Specifically, we calculated an Overall age-relatedness score (OA score) for each pathway by summing its odds ratio with all diseases. We then created a heatmap of the cellular component with the highest OA score and its correlation with the ten diseases, as depicted in Figure 4A. Each square's number represents the predictability of the corresponding pathway for the related disease. For easier visualization, we have scaled the odds ratio between 0 and 1, where a square's color closer to purple indicates higher corresponding odds.

Interestingly, many cellular component aging indexes' relationships with diseases are not uniformly distributed. The cellular components shown in the figure are primarily associated with the diseases listed on the right half, including Atherosclerosis, Depression, Parkinson's Disease, Severe COVID-19, and Rheumatoid Arthritis.

We examined the correlation between each pathway, as shown in Figure 4B. Each pathway, along with its predictive ability for 10 diseases and its odds ratio, forms a 10×1 variable. We utilized Pearson correlation to calculate the correlation of all pathway combinations, representing the correlation coefficient rho as a heatmap. Squares closer to yellow indicate correlation coefficients near 1, while rose-colored squares indicate coefficients closer to -1.

From the figure, it is evident that most cellular component aging indices have a positive correlation. However, certain pathways, specifically chromosomal region, RNA polymerase II transcription regulator complex, transcription regulator complex, and nuclear chromosome, show a negative correlation.

In several age-related diseases, the cellular component aging index forms two distinct groups, sometimes displaying a negative correlation. We selected three representatives from each group and analyzed their relationship with 10 diseases, resulting in a clustergram as demonstrated in Figure 5A. Interestingly, these six representative cellular component aging indices distinctly categorize all 10 diseases into two primary groups, implying the existence of two types of age-related diseases.

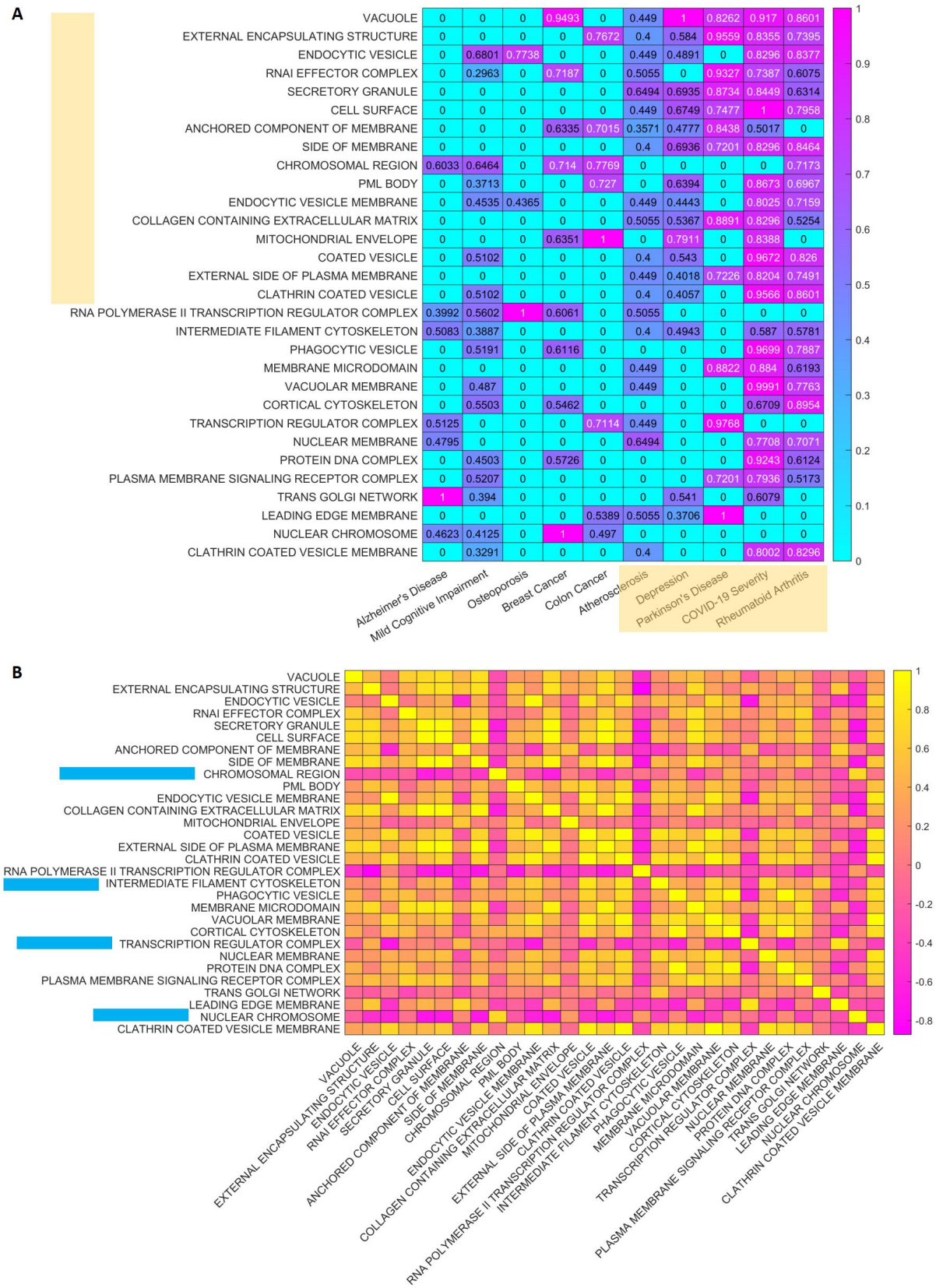


Figure 4 The Organelle Aging Index is Linked to Multiple Age-Related Diseases. A. The correlation between the cellular component pathway index and ten types of age-related diseases.B. the correlation between each pathway.

The first type comprises Alzheimer’s Disease, Mild Cognitive Impairment, Breast Cancer, Colon Cancer, and Osteoporosis. These diseases are associated with aging related to the nucleus, chromosome, and DNA. The second type includes Parkinson's Disease, Depression, Atherosclerosis, COVID-19 Severity, and Rheumatoid Arthritis, and is characterized by aging related to the cytoplasm, cell membrane, and extracellular space.

Notably, Alzheimer's and Parkinson's diseases, both neurodegenerative diseases, fall under two distinct categories in terms of organelle aging or protein complex aging. We propose to name these two types of aging "nucleus aging" and "cytoplasm aging," or "yin aging" and "yang aging," respectively.

From a cellular adaptation perspective, cytoplasm aging mainly involves the decline in the ability to respond to external stimuli. This is exemplified by Parkinson's disease, where abnormal temperature perception is common. COVID-19 severity shares this characteristic, with some patients experiencing severe symptoms due to a decline in the ability to respond, particularly in cell membrane-dependent biological processes.

After cell populations respond and adapt to environmental stimuli, those with better adaptation or evolutionary advantages are recorded in epigenetic events like DNA methylation. As a result, cells that assist the body to adapt better to environmental stimuli increase in proportion, and their representative DNA methylation patterns dominate our test samples. Therefore, we hypothesize that nuclear aging primarily reflects the decline of this information storage mechanism, while cytoplasmic aging represents a decrease in the cell's functional execution capabilities.

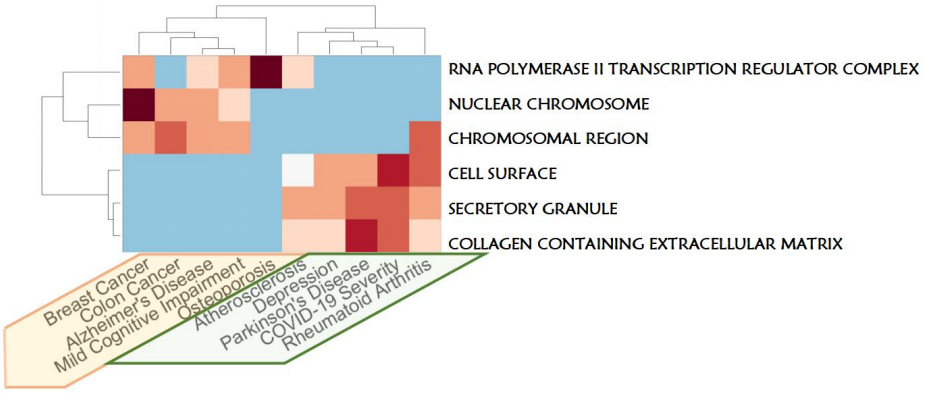
Discussion

Our study introduces a framework that expands the biological aging clock from 10 organs to over 3000 cellular pathways. The traditional aging clock, which assigns a single value to the entire human body and predicts disease and mortality risk [2], lacks the ability to predict organ-specific diseases. A recent study introduced '10 organ clocks', which link plasma proteome aging signatures with health conditions. These 'organ clocks' capture the aging of each organ and can predict diseases specific to those organs [10]. Our paper delves deeper into the investigation of aging, calculating aging from the organ level down to the cellular, organelle, and even protein complex levels, such as the RNA transcription regulator complex and secretory granule discussed in this paper. The expansion from 10 to over 3000 dimensions opens up a vast area for biomarker discovery and therapeutic target identification.

The "hallmarks of aging" is a concept curated by scientists, offering a comprehensive summary of our understanding of the aging process [21]. This article provides a new data-driven perspective on these hallmarks, beginning with the common patterns and classifications of 10 age-related diseases. Firstly, pathways reported in this article that have predictive capabilities for diseases all align with the characteristics outlined in the aging hallmarks. For instance, DNA repair predicting Alzheimer's disease and breast cancer involves genomic instability, a feature of the aging hallmarks. Protein folding, which predicts colon

cancer, is part of the loss of proteostasis, another aging hallmark. Mitochondrion organization, which predicts major depressive disorders, aligns with mitochondrial dysfunction, also a hallmark of aging. Cell-cell communication, which predicts rheumatoid arthritis, falls under altered intercellular communication, a further aging hallmark. Additionally, our results reflect characteristics summarized in the hallmarks of health [22]. For example, in our cellular component analysis, we found many links between membrane aging and disease. These membranes are part of spatial compartmentalization (integrity of barriers and containment of local perturbations), a feature in the hallmarks of health. The classification of 10 age-related diseases into nucleus aging and cytoplasm aging proposed in this article, if validated in more age-related diseases, will offer new data-driven tools for understanding the common features and classification of diseases at the level of organelles and molecular complexes.

A



B

Concept Dimentions	Aging type 1	Aging type 2
Disease	Alzheimer's Disease Mild Cognitive Impairment Breast Cancer Colon Cancer Osteoporosis	Parkinson's Disease Depression Atherosclerosis COVID-19 Severity Rheumatoid Arthritis
Cellular Componet Aging signatures	Nucleus,Chromosome, DNA	Cytoplasm,Cell membrane Extracellular space
Cellular Componet roles	Information Storage for Recording the "learned skills" of cell response to Environmental Stimuli	Functional Execution for Responding to Environmental Stimuli
Naming	**Nucleus Aging**	**Cytoplasm Aging**
Naming ref to TCM (Traditional Chinese Medicine)	***Yin* Aging**	***Yang* Aging**

Figure 5 The cellular component aging index classifies 10 age-related diseases into two categories: nucleus aging and cytoplasm aging. A. The clustergram clearly groups these 10 age-related diseases into two clusters. B. A comparative analysis of the two types of aging.

The deep age clock model suggested in this article could significantly contribute to research and practice in healthy aging. It could serve as a omics counterpart to the World Health Organization's (WHO) intrinsic capacity (IC) concept. Traditional models, which primarily focus on diseases, often neglect the complex needs of older individuals, resulting in fragmented care. The IC concept from WHO addresses determinants of functional ability and promotes healthy aging. It provides a health assessment framework considering five core domains: locomotor, sensory, vitality, psychological, and cognition. However, standardization of IC measures across different domains, which rely heavily on phenotype measurement, is lacking and varies across studies [23].

We're introducing the concept of 'capomics', referring to the 'omics of capability'. For any pathway or ontology, whether it describes a macroscopic biological function or a specific protein complex function, we can compute an aging index, also known as the Pathway Aging Index (PA). We normalize this between 0 and 1, defining capability as 1- PA. This allows us to quantify the function of any pathway or ontology. To differentiate this from capacity, as defined in the IC concept, we use the term 'capability'. Therefore, we can determine the capability of any biological function that can be described by a gene set or protein complex.

One significant advantage of the capomics method is its high dimensionality and data-driven nature, which can encompass multi-scale measurements from micro to macro. By using a single blood or saliva sample and genome-wide DNA methylation profiling, we can quantify an individual's capabilities from microscopic protein complexes to macroscopic angiogenic shapes. For instance, individuals with higher aging indices related to the heat response pathway in Parkinson's disease are more likely to exhibit abnormal body temperature regulation and other symptoms. It's worth noting that body temperature control is a common symptom of Parkinson's disease.

The second feature of the capomics method is its convenience and feasibility. A comprehensive IC assessment would require several hours of collaboration between medical staff and patients, and it includes some subjective evaluation scales. In contrast, capomics tests may only require a single collection of whole blood or saliva.

The limitations of this article include the study of a relatively small number of age-related diseases. Testing with a broader range of disease types and a larger number of clinical samples is necessary. Additionally, it would be beneficial to investigate whether the method proposed in this article can accurately reflect drug treatment efficacy and their mechanisms of action. This includes tracking changes in aging intervention and the disease recovery process.

Conclusions

'Next Generation Aging Clock Models' use DNA methylation data for disease prediction, such as Alzheimer's and breast cancer. They classify diseases into nucleus and cytoplasm aging types, aiding research and personalized interventions. The study expands the aging clock to 3000 pathways, deepening our understanding of aging. It introduces 'capomics', an omics equivalent to WHO's intrinsic capacity (IC) concept, for quantifying pathway functions.

Conflicts of Interest

DeepoMe is a commercial organization developing explainable artificial intelligence (XAI) solutions for health tracking, intervention and drug repurposing in aging related diseases.

Acknowledgement

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