Press Release

Keio University

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Keio University School of Medicine

A Cardiovascular Biomarker and Plasma Albumin Predict the Chance of Living to Supercentenarian Ages

Scientists have identified that cardiovascular biomarker, NT-proBNP[1], is a strong predictor of survival to the highest age. They showed that low NT-proBNP is more relevant for exceptional survival beyond age 105 than inflammation, organ reserves, and lipid and glucose metabolism.

For the first time, a team of experts has explored which of the molecular markers that represent various biological processes may contribute to survival to the highest ages, namely 110 years of age. The team comprised researchers from the Keio University School of Medicine Center for Supercentenarian Medical Research (Director & Professor: Hideyuki Okano, http://www.keio-centenarian.com/english), the Kumamoto University Graduate School of Medical Sciences Department of Molecular Genetics (Professor Yuichi Oike), and the Gifu Pharmaceutical University Department of Biomedical Pharmaceutics, Laboratory of Clinical Pharmaceutics (Professor Tetsuo Adachi).

The team found that NT-proBNP is strongly associated with life expectancy, especially in those aged 105 or older, and that the lower the NT-proBNP in one's blood, the higher the chance that individual has of living until the age of 110 or beyond. In contrast, a decrease in plasma albumin, a biomarker for nutrition, and an important predictor of life expectancy in the elderly, was associated with all-cause mortality across all age groups.

This study has revealed some of the biological characteristics of the oldest old approaching the current limit of the human lifespan and may contribute to future research for the prevention and delay of cardiovascular disease, the risk for which increases as society continues to age.

The results of this study were published online on July 30 in *Nature Communications*, an open access journal supported by Springer Nature.

1.Research details

With the steady increase in life expectancy in recent decades, the number of centenarians has increased dramatically worldwide. Still the number of supercentenarians people who have reached their 110th birthday remains extremely rare across the globe, suggesting the presence of a potential biological barrier to survival beyond that age.

The research team hypothesized that survival to the highest ages is supported by protection against cardiovascular diseases, since they are the leading cause of death in old age, and the cardiovascular system is intrinsically more susceptible to increased oxidative stress and inflammation that accompany aging.

The team used a comprehensive dataset of 1,427 of the oldest people in Japan, comprising 36 supercentenarians (110 years or older), 572 semi-supercentenarians (105–109 years), 288 centenarians (100–104 years), and 531 people aged 85-89 years.The team analysed the association of 9 biomarkers[2] reflecting cardioprotection, inflammation, and renal and liver functions with overall and age-specific mortality, compared with traditional risk factors and clinical and subclinical conditions such as ECG abnormalities.

The team identified four prognostic biomarkers in blood—NT-proBNP (neurohormone), interleukin-6 (inflammation), cystatin C (renal function), and cholinesterase (liver function)—that predict all-cause

mortality in the entire cohort of oldest-old people. Among these, NT-proBNP in particular is strongly associated with survival beyond105 years of age. In contrast, plasma albumin, a biomarker of nutrition, is consistently associated with mortality across all age groups.

NT-proBNP is one of the most reliable biomarkers of heart failure, the leading cause of death in old ages worldwide. The production of this molecule is also known to be elevated in a variety of cardiovascular diseases including heart failure, coronary heart disease, and atrial fibrillation. In addition, NT-proBNP in the blood increases with age and renal dysfunction.

The team found that circulating NT-proBNP increased with age in all the cohorts that survived to 100 years and older, but those who survived beyond 110 years of age showed lower levels of NT-proBNP at any given age of assessment compared to younger age cohorts.

Dr. Yasumichi Arai from Keio University School of Medicine who led this study said, "Both centenarians and supercentenarians are characterized by low cardiovascular risks[3] such as low cholesterol levels, low prevalence of diabetes, and left ventricular hypertrophy on ECG. However, people who are successful in keeping NT-proBNP low have the best chance to break through the 110-year lifespan ceiling."

Dr. Arai added, "Interestingly, circulating NT-proBNP is elevated with age, even in centenarians without clinical or subclinical cardiovascular disease. Our data suggests that intrinsic aging in the cardiovascular system and possibly the renal system may ultimately deteriorate hemodynamic homeostasis, which eventually limits current human longevity.

"Supercentenarians, by virtue of a postponed age-related increase in circulating NT-proBNP, may be equipped with efficient mechanisms for delaying the processes of cardiovascular aging."

"Aging is increasingly recognized as a major risk factor of cardiovascular diseases. The prevalence of heart failure with preserved ejection fraction, for example, increases with age. However, no effective treatment has been found for this cardiovascular disease. Investigation of the cardiovascular system of supercentenarians may provide important insight to help develop pharmacological strategies for these formidable diseases."

Because of the extremely small number of persons who live past 110 years even in countrieswith high life expectancy, recruiting a substantial number of supercentenarians took more than 10 years. During the study period, 123 participants born around 1900 died at ages 110 or higher. These supercentenarians achieved so-called "natural longevity" without benefiting from the development of innovative pharmaceuticals such as statins[4] and renin-angiotensin system inhibitors[5].

"Unmedicated supercentenarians, who represent the relatively natural life course of the longest living humans, may serve as a valuable index group for future studies of supercentenarians, who are more likely to have received medications with potential anti-aging effects."

The data was collated by combining three community-based group studies: the Tokyo Centenarians Study (reference 1), the Japanese Semi-Supercentenarians Study (reference 2) and the Tokyo Oldest Old Survey on Total Health (reference 3).

The aim of this study was to identify specific biomarkers conducive to exceptional survival to supercentenarian age, which may provide molecular insights into the mechanisms that protect against aging-related diseases.

Given the worldwide prolongation of life expectancy and the increasing proportion of older individuals in the total population, understanding the biological effects of aging on major organ systems and the counter-regulatory mechanisms associated with high and exceptional longevity may help to extend healthy lifespans for the wider population.

Professor Nobuyoshi Hirose, founder of the Tokyo Centenarians Study and the Japanese Semi-Supercentenarians Study, added, "Unravelling the molecular and genetic basis of slower cardiovascular

aging in supercentenarians may contribute to the identification of therapeutic targets for the prevention or delay of cardiovascular diseases in aging."

The results of this study were published online on July 30 in *Nature Communications*, an open-access journal supported by Springer Nature.

2. Notes

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·Program for an Integrated Database of Clinical and Genomic Information:
"Development of clinical genome database of dementia"
·Platform Program for Promotion of Genome Medicine:
"Metabolomics analysis for development of liquid biopsy by using sera from disease patients"

3. Research Paper

Title：Associations of Cardiovascular Biomarkers and Plasma Albumin with Exceptional Survival to the Highest Ages

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[Glossary]

[1] **NT-proBNP**
Abbreviation for N-terminal pro-brain natriuretic peptide. The concentration of NT-proBNP in blood, which arises with the decomposition of pro-brain (type B) natriuretic peptide (BNP) secreted due to cardiac stress, reflects cardiovascular function and is mainly used in diagnosing and assessing the severity of heart failure.

[2] **Biomarker**
Biomarkers are biologically-derived molecules contained in blood and are a biological index for the quantitative evaluation of the function and metabolic state of organs such as the heart, liver and kidneys.

[3] **Cardiovascular Risks**
Factors that increase the risk of developing cardiovascular diseases, such as smoking, hypertension, hyperlipidemia, diabetes, and chronic kidney disease.

[4] **Statins**
A generic term for HMG-CoA reductase inhibitors. Statins reduce blood cholesterol levels by specifically

inhibiting HMG-CoA reductase, which regulates the rate of cholesterol synthesis. Statins are the most widely used lipid-lowering drugs in the world because they have a stronger cholesterol-lowering effect than pre-statin lipid-lowering drugs, and have anti-atherogenic and help prevent the effects of coronary artery disease.

[5] **Renin-Angiotensin System Inhibitors**

Renin-angiotensin system inhibitors include ACE inhibitors and ARBs and are drugs that lower blood pressure by inhibiting the renin-angiotensin-aldosterone system (RAAS), which regulates blood pressure. In addition to their antihypertensive effect, they have been shown to improve the prognosis of patients with heart failure, and have a renal protective effect as well as anti-atherosclerotic effects, and are a typical therapeutic agent for cardiovascular disease.

[References]

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