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# Welllderly study finds link between cognitive decline genes and healthy aging

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An eight-year-long accrual and analysis of the whole genome sequences of healthy elderly people, or "Welllderly," has revealed a higher-than-normal presence of genetic variants offering protection from cognitive decline, researchers from the Scripps Translational Science Institute (STSI) reported today in the journal *Cell*.

The initial findings from the Welllderly Study suggest a possible link between long-term cognitive health and protection from chronic diseases, including cancer, heart disease and diabetes, which account for 90 percent of all deaths in the United States and other industrialized nations and more than 75 percent of health care costs.

"The Welllderly, as we've defined, are exceptional individuals who live into their ninth decade and beyond without developing a significant chronic medical condition," said STSI Director Eric Topol, M.D., who is one of the study's senior authors. "Our findings indicate that protection from cognitive decline is associated, not necessarily cause and effect, with healthspan. Since healthspan is woefully understudied, much more work in large numbers of individuals across all ancestries is desperately needed. For this reason, we have made all the genomic data available to the research community and public to help spawn further research."

Results of the Welllderly Study were published online today by *Cell*. The report also will appear in the journal's May print edition.

STSI is a National Institutes of Health-sponsored site led by Scripps Health in collaboration with The Scripps Research Institute. This innovative research partnership is leading the effort to translate wireless and genetic medical technologies into high-quality, cost-effective treatments and diagnostics for patients.

## More than 1,400 enrolled in the ongoing study

STSI researchers launched the Welllderly Study in 2007 in hopes of unlocking the genetic secrets behind lifelong health. The ongoing project has enrolled more than 1,400 people from across the country ranging in age from 80 to 105 who have not developed any chronic medical conditions or diseases including cancer, stroke, Alzheimer's, Parkinson's disease, diabetes and heart attack.

"This study is exciting because it is the first large one using genetic sequencing to focus on health," said Stanford University Department of Genetics Chairman Michael Snyder, Ph.D., who was not involved with the research. "Most of the world's scientists are studying disease, but what we really want to understand is what keeps us healthy. That is what the Welllderly Study is all about."

John Rawlings, 90, of San Diego is one of the study's participants. The Indiana native and World War II veteran started playing softball in his 70s and was inducted into the National Senior Softball Hall of Fame in 2009. He also is an avid reader.

"When I turned 90, they said, 'Let's have a big party,'" Rawlings said. "I told them, 'You'd better wait until I turn 100.'"

For the study, researchers sequenced the whole genomes of 600 study participants and compared their DNA with genetic data gathered from 1,507 adults by Inova Translational Medicine Institute as part of a separate study. The ITMI cohort represented the general population. All of the genomes were mapped using the Complete Genomics sequencing platform.

After filtering to control for ethnic differences and blood relatedness, downstream DNA analyses were conducted on the genomes of 511 Welllderly individuals and 686 ITMI individuals. Researchers ended up analyzing 24,205,551 individual gene variants in both groups.

## Lower risks for Alzheimer's and coronary artery disease

The Welllderly group had a significantly lower genetic risk for Alzheimer's and coronary artery disease, researchers found. However, no difference was found between the two groups in genetic risk for cancer, stroke or type 2

diabetes, suggesting protective behaviors or other genetic characteristics might be at play among the Welllderly.

"We didn't find a silver bullet for healthy longevity," said Ali Torkamani, Ph.D., director of genome informatics at STSI and one of the study's co-authors. "Instead, we found weaker signals among common as well as rare variant sites, which collectively suggest that protection against cognitive decline contributes to healthy aging."

Of particular interest was a group of ultra-rare coding variants found among 10 Welllderly individuals in the *COL25A1* gene, which encodes for a major component of amyloid plaques found in the brains of Alzheimer's disease patients. None of the coding variants were found among the ITMI individuals.

"Those gene variants might offer a pathway for the development of new treatments for Alzheimer's," Torkamani said.

"For many decades, we have searched for the genetic causes of disease in sick individuals," noted founding director of the Icahn Institute for Genomics and Multiscale Biology at Mount Sinai Eric Schadt, Ph.D., who was not involved with the STSI research. "The Welllderly Study presents an attractive alternative by studying those who are well in order to uncover the solutions nature has provided to protect us against disease. The initial discoveries around protective factors for Alzheimer's disease and coronary artery disease demonstrate the keys the Welllderly may hold in unlocking ways in which we all may live healthier lives."

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Source:  
Scripps Research Institute

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