100-plus Study: Protection against cognitive decline.

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Research question and background

The focus of AD research is and has been on the amyloid cascade. However, a puzzling problem in the AD field is that with increasing age, a growing number of cognitively normal individuals present significant Amyloid-β plaques accumulation in their brains. This suggests that these cognitively healthy elderly are somehow resilient to these pathologies.

It is, therefore, essential to gain a deep comprehension of molecular processes that maintain cognitive health during ageing. For this we invest in the in-depth molecular profiling of the genomes and brain tissues of cognitively healthy centenarians (CHCs). Detailed knowledge of the processes that maintain cognitive health or protect against cognitive decline might reveal where and how we can intervene in processes that lead to cognitive decline.

Methods and tissues used

To create a resource of genetic variants that protect against cognitive decline we initiated the 100-plus Study at the VUmc Alzheimer Center (www.100plus.nl) in 2013. In this study we collect a unique cohort of genomes and matching brain tissues from proven cognitively healthy centenarians (CHCs). The combined assets of (i) the growing number of Dutch CHCs (currently 2,200, half of whom live independently), (ii) the excellent autopsy and tissue quality provided by the Dutch Brain Bank, and (iii) the availability of state-of-the-art biomolecular techniques at the VU and VUmc, puts us in an excellent position to investigate the healthy brain.

Recruitment flyer

We will contrast the genetic elements from these healthy centenarians to those from patients suffering from severe Alzheimer's Disease (AD), representing the opposite end of the cognitive spectrum. Further, the unique availability of brain tissues allows us to focus only on those genes that are differentially expressed in brain cells. For this, we will contrast the CHC brains to early onset AD brains that were previously donated to The Netherlands Brain Bank (NHB). The combined genetic and proteomic aspects of this approach will maximize the power of a genetic analysis, allowing successful detection of genetic elements associated with cognitive outcome in relatively small sample sizes.

Results and conclusion

Since the start in 2013, we have included 107 centenarians in the study. Because centenarians have seen others suffer from cognitive decline, they are inclined to help advance dementia research. We find that ±30% of the CHCs generously agree to post-mortem brain donation. So far, 7 have been collected. We expect to have access to at least 45 brains in the coming two-three years.