EDITORIAL

Longevity Gene *KLOTHO* and Alzheimer Disease—A Better Fate for Individuals Who Carry *APOE* ε4

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The apolipoprotein E ε4 (*APOE4*) allele is the strongest genetic risk factor for Alzheimer disease (AD), the most common neurodegenerative condition. Unfortunately, *APOE4* is not rare. Approximately 23% of the US population carries an allele. One copy increases risk of developing AD by 3-fold; 2 copies increases it by more than 12-fold. The *APOE4* allele shortens the time to disease onset and reduces survival[1,2] in both sporadic and familial AD. Beyond AD, *APOE4* increases the likelihood of cognitive decline in patients with other neurologic disorders,[3] elderly people who are clinically normal,[4] and even patients with head trauma as putatively mild as heading a ball in soccer.[5] Neuroanatomic differences with *APOE4* have been detected in AD-relevant brain regions in adolescence[6] and as early as infanthood.[7] Remarkably—despite the lifelong influences of *APOE4*—not all who carry the allele are fated for AD.

Related article

Klotho, daughter of Zeus, is the Greek Fate who spins the thread of life and the eponym for a circulating longevity hormone with emerging relevance for clinical neurology. Klotho is secreted from the kidney and choroid plexus and exerts pleiotropic functions ranging from autophagy to modulation of insulin and *N*-methyl-D-aspartate receptor signaling. Discoveries in mice reveal that elevating klotho extends life span,[8] enhances synaptic functions,[9,10] improves cognition in aging,[9,10] and boosts resilience to AD-associated toxicity.[11] Humans, too, have klotho, and we now wonder whether circulating levels may matter in aging and brain health. We are born with levels more than 7-fold higher compared with adulthood levels. Then, through the process of aging, klotho levels decline, and precipitously so in people with neurodegenerative diseases like AD. Intriguingly, aging individuals who are clinically normal and have higher serum klotho show enhanced functional connectivity between brain regions selectively vulnerable to degeneration in AD,[12] another indication that this Fate may wield her powers to bolster brain health.

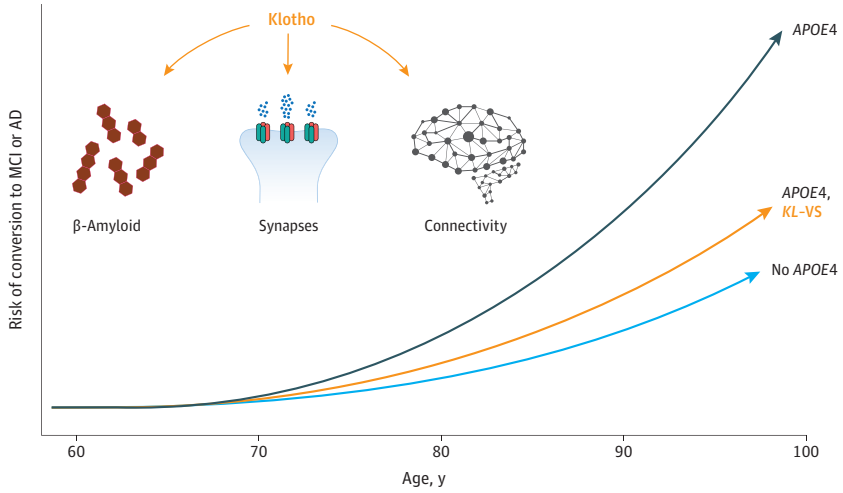
While all individuals carry the *KLOTHO* (*KL*) gene that codes for the klotho hormone, approximately 20% carry a functional variant termed *KL*-VS, and this enables more extensive study of klotho in human health. Two amino acid substitutions in human *KL*, F352V (V) and C370S (S), segregate together as *KL*-VS and alter cellular klotho secretion[13] or may change its functions. Carrying 1 copy of *KL*-VS increases circulating klotho,[9,14] while carrying 2 decreases it.[14] One copy of *KL*-VS (in other words, *KL*-VS heterozygosity) is associated with longer life,[13] robust frontal brain volume,[14] and better executive cognition[9,14] in some but not all aging populations. The beneficial influence of *KL*-VS in aging and brain health raises a timely question: could carrying *KL*-VS counter the *APOE4*-AD risk?

In this issue of *JAMA Neurology*, Belloy et al[15] probed the link between *KL*-VS heterozygosity and the *APOE4*-AD risk with a high-powered meta-analysis including more than 20 000 individuals across a full age span of individuals 60 years and older in 22 independent research cohorts, collectively representing a spectrum of normal cognitive aging, mild cognitive impairment (MCI), and AD. In addition to power, their work adds the variables of life stage, AD conversion risk, and pathological β-amyloid (Aβ) to a new understanding of the *KL*-VS–*APOE4* association. Remarkably, they found that in individuals who carry *APOE4*, *KL*-VS heterozygosity was significantly associated with (1) reduced risk for AD, (2) reduced risk of conversion to MCI or AD (**Figure**), and (3) reduced Aβ biomarkers measured by brain imaging and cerebrospinal fluid. Curiously, benefits of *KL*-VS heterozygosity on all AD measures were limited to individuals who carry *APOE4* and not observed in those who do not carry *APOE*4. Furthermore, association of *KL*-VS with AD risk and Aβ were most robust in the group aged 60 to 80 years, the life stage during which individuals who carry *APOE*4 show the strongest AD risk. Finally, careful age-at-onset analyses revealed that *KL*-VS heterozygosity was associated with reduced risk of conversion to MCI or AD beginning around age 77 years in individuals who carry *APOE4* (Figure). It is important to note that *KL*-VS homozygosity, a rare genotype leading to lower klotho levels and decreased life span, did not associate with protection against the *APOE4*-AD risk.

It is noteworthy that the *KL*-VS–*APOE4* association was conserved across populations in North America and parts of Europe, despite inherent variations caused by geography and environmental conditions that can obscure genetic associations. However, the study's inclusion of only non-Hispanic Northwestern European individuals to avoid population confounding from known allele frequency differences of both *APOE4* and *KL-VS* limits the generalizability of the findings worldwide or across diverse ancestry. Furthermore, the lack of measurements of the klotho hormone itself from the serum or cerebrospinal fluid of individuals restricts interpretation of the findings, particularly since klotho levels might represent a higher resolution biomarker in assessing the *APOE4*-AD risk. These limitations represent exciting future directions for the field to pursue.

In short, despite the stated limitations, the Belloy et al[15] meta-analysis provides strong evidence that individuals who carry *APOE4* are not uniformly fated to develop AD and specifically establishes a protective role of *KL*-VS heterozygosity in the *APOE4*-AD risk. This work is important because it car-

Figure. Attenuation of Apolipoprotein E ε4 (*APOE4*)–Associated Alzheimer Disease Risk With *KLOTHO* Variant (*KL-VS*) Heterozygosity



Heterozygosity in *KL*-VS, which leads to higher circulating klotho levels, associates with decreased risk of conversion to mild cognitive impairment (MCI) and Alzheimer disease (AD) among individuals who carry *APOE4*. A hypothetical model of klotho benefits that could counter *APOE4* include protection against pathological β-amyloid production or deposition, enhanced synaptic functions, and increased brain connectivity. This is important because *KL*-VS status could mitigate *APOE4* risks for Alzheimer disease and could be used to further stratify individuals who carry *APOE4* in clinical trials for the disease. Klotho itself could represent a therapeutic for the prevention or treatment of Alzheimer disease in individuals who carry *APOE4*.

ries several implications for neurology, clinical trials, and translational research. For personalized genomics, *KL*-VS status should integrate into knowledge that both lifestyle and genetics can negate or at least mitigate harmful influences of *APOE4*. In light of this, we might consider an individual's *KLOTHO* genotype when counseling individuals who carry *APOE4* about their prognosis for AD. In clinical trials using *APOE4* for trial enrichment, further selection of individuals who carry *APOE4* without *KL*-VS could define a population more likely to convert to AD and thus increase detection of a therapeutic benefit. In translational research, understanding how klotho itself or its biological pathways may counter *APOE4* could lead to monumental progress in the future treatment of AD.

The specificity of *KL*-VS benefits on AD in individuals who carry *APOE4* is striking and suggests a yet-unstudied interaction between biological pathways of the klotho and APOE4 proteins. Could klotho attenuate APOE4-mediated disruption of synaptic and network dysfunction or counter APOE4-induced increases in Aβ (Figure)? Klotho is associated with network function in humans and stimulates enhanced synaptic transmission in mice, even without APOE4; however, the intriguing link between *KL*-VS and the *APOE4*-AD risk raises many questions. Does klotho more robustly and preferentially engage APOE4-specific molecular pathways in bolstering the brain? Are these pathways specific to AD, or do they extend to other neurologic diseases for which *APOE4* also increases risk?

In summary, the study by Belloy et al[15] is timely and provides solid evidence that the Fate Klotho, in biological form, may mitigate risks for AD in individuals who carry *APOE4*. When and how the benefits of *KL*-VS heterozygosity counter lifelong risks associated with *APOE4* remain to be determined. Nonetheless, in a world where genetics informs brain landscapes, individual trajectories, and clinical trial design, *KLOTHO* may prove essential. Furthermore, if levels of the klotho hormone matter, we may outwit our genetics through exercise, which increases klotho, and decreased chronic stress, which decreases it. The klotho hormone itself could represent a new treatment. Applying our growing knowledge of klotho to *APOE4* and AD could ultimately pave the path to novel therapeutics for individuals who carry *APOE4*.

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