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Newly Evolved, Uniquely Human Gene Variants Protect Older Adults from Cognitive Decline

Humans evolved unique gene variants that protect older adults from neurodegenerative disease, thus preserving their valuable contributions and delaying dependency

Many human gene variants have evolved specifically to protect older adults against neurodegenerative and cardiovascular diseases, thus preserving their contributions to society, report University of California, San Diego School of Medicine researchers in the November 30 issue of *Proceedings of the National Academy of Sciences*.

Elders contribute to the fitness of younger individuals by caring for grandchildren and passing down important cultural knowledge. Credit: USDA

"We unexpectedly discovered that humans have evolved gene variants that can help protect the elderly from dementia," said Ajit Varki, MD, Distinguished Professor of Medicine and Cellular and Molecular Medicine at UC San Diego School of Medicine, adjunct professor at the Salk Institute for Biological Studies and co-director of the UC San Diego/Salk Center for Academic Research and Training in Anthropogeny (CARTA). "Such genes likely evolved to preserve valuable and wise grandmothers and other elders, as well as to delay or prevent the emergence of dependent individuals who could divert resources and effort away from the care of the young." Varki led the study, along with Pascal Gagneux, PhD, associate professor of pathology and associate director of CARTA.

The standard model of natural selection predicts that once the age of reproduction ends, individuals die. That's because selection early in life strongly favors variants that benefit reproductive success, even at the cost of negative consequences late in life — one major

reason we age. This is indeed the case in almost all vertebrates. Humans (and certain whales) are an exception to this rule, living decades beyond reproductive age. Such elders contribute to the fitness of younger individuals by caring for grandchildren and also by passing down important cultural knowledge. Age-related cognitive decline compromises these benefits, and eventually burdens the group with the need to care for dependent older members.

In this first-of-its kind discovery, Varki, Gagneux and their teams initially focused on the gene that encodes the CD33 protein. CD33 is a receptor that projects from the surface of immune cells, where it keeps immune reactions in check, preventing “self” attack and curtailing unwanted inflammation. Previous studies suggested that a certain form of CD33 suppresses amyloid beta peptide accumulation in the brain. Amyloid beta accumulation is thought to contribute to late-onset Alzheimer’s disease, a post-reproductive condition that uniquely affects humans and is aggravated by inflammation and cerebral vascular disease.

The researchers compared CD33 regulation in humans and our closest living relatives, chimpanzees. They found that levels of the CD33 variant that protects against Alzheimer’s are four-fold higher in humans than chimpanzees.

They also found human-specific variations in many other genes involved in the prevention of cognitive decline, such as APOE. The ancestral form of the gene, APOE4, is a notorious risk factor for Alzheimer’s and cerebral vascular disease. But this study finds that variants APOE2 and APOE3 seem to have evolved to protect from dementia. All of these protective gene variants are present in Africa, and thus predate the origin of our species. This finding is in keeping with the valuable role of the elderly across human societies.

“When elderly people succumb to dementia, the community not only loses important sources of wisdom, accumulated knowledge and culture, but elders with even mild cognitive decline who have influential positions can harm their social groups by making flawed decisions,” Gagneux said. “Our study does not directly prove that these factors were involved in the selection of protective variants of CD33, APOE and other genes, but it is reasonable to speculate about the possibility. After all, inter-generational care of the young and information transfer is an important factor for the survival of younger kin in the group and across wider social networks or tribes.”

Additional study co-authors include Flavio Schwarz, Stevan A. Springer, Tasha Altheide, Nissi M. Varki, all of UC San Diego.

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