Genes that may protect against dementia

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"Survival of the fittest" is one of the most misunderstood terms in biology. Evoking images of physical prowess, it actually refers to an individual inheriting traits that increase the chances of having fertile offspring, such as brilliant plumage or a high sperm count. But according to an intriguing study published recently in *Proceedings of the National Academy of Sciences*, for we humans, natural selection may favor grandparents who enjoy what appears to be genetic protection against

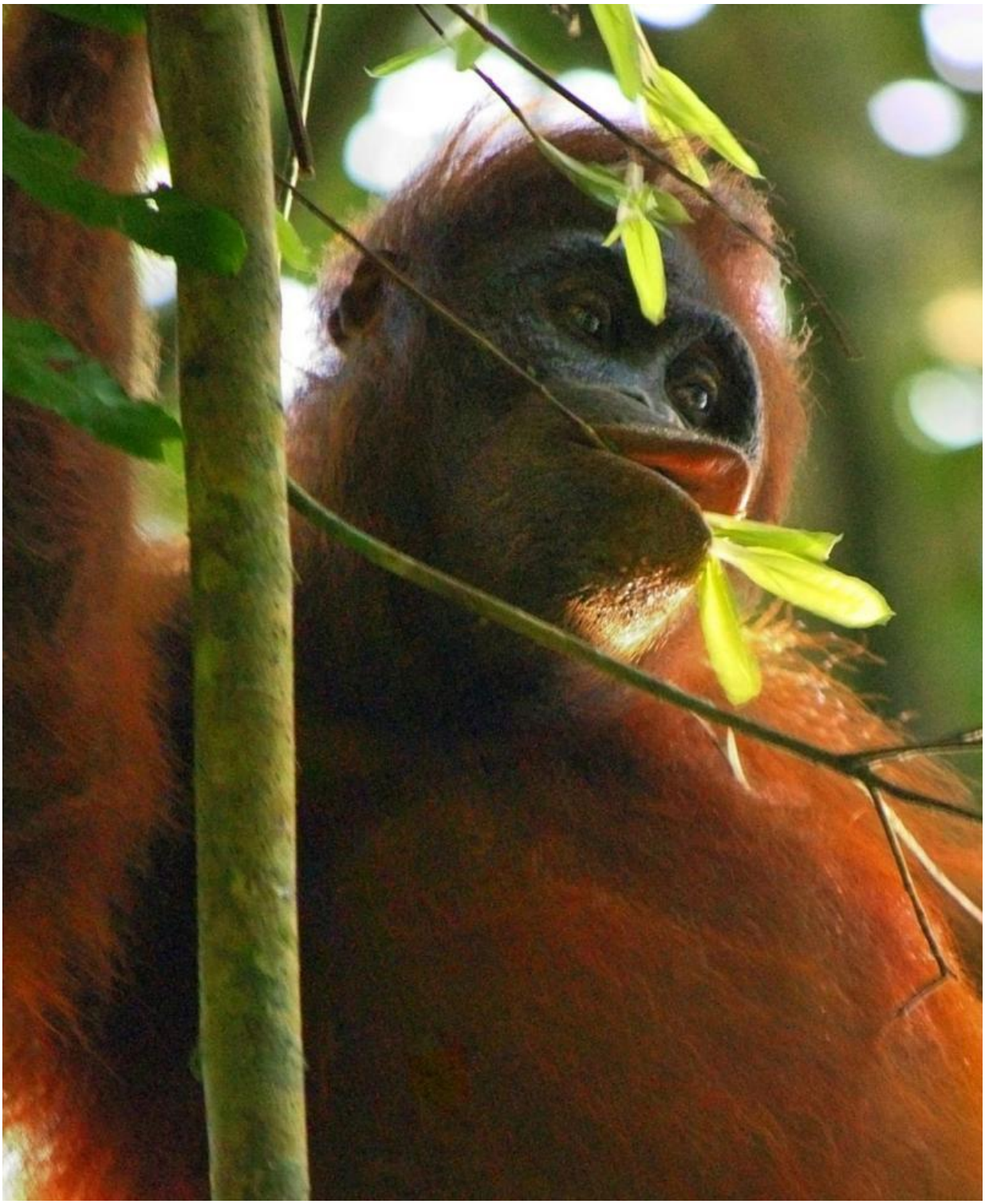
dementia. The reasoning: maintaining cognition and memory well into old age enables elders to impart their wisdom to and care for their grandchildren, while elders with dementia require care themselves.

The granny hypothesis fits in well with a decades-old idea called kin selection. That is, individuals can perpetuate their genes not only by having offspring, but also by easing survival of younger relatives, with whom they share gene variants. This seeming altruism, for example, is why an ant gives its life to form part of a bridge so that its relatives can traverse a gap in the terrain, or why a squirrel screeches out a warning even though doing so costs it its life. Human grandparents who can think clearly, the hypothesis holds, increase the odds of survival of their children's children by being able to teach them life skills, metaphorical ant bridges.

Humans and toothed whales are the only mammals that live past the age of reproductive utility. Orcas can survive post-menopause, supposedly, because they know the environment well enough to teach young whales how to successfully forage when food is scarce. Humans may have gone down the same evolutionary road until late-onset dementia of the Alzheimer's type arose, which is apparently unique to us. It impaired the ability of some elders to help young relatives. (I don't know how one studies dementia in other mammals, although I think I've seen it in cats.)

To address this hypothesis, Ajit Varki, MD, Pascal Gagneux, PhD, and colleagues at the University of California, San Diego School of Medicine looked for relatively new mutations that might counteract a tendency towards dementia. They found it first in the gene CD33, which encodes a receptor that keeps inflammation and the immune response in line. The "C" allele is associated with late-onset dementia but the "A" allele protects cognition by enabling microglia (a type of brain cell) to sop up excess amyloid beta, one of the sticky proteins that accumulates in Alzheimer's. Chimps, bonobos, gorillas, Neanderthals, and Denisovans

all have the "C" allele, with some lucky modern humans the only primates examined to have the protective "A" allele. The A variant is thought to have emerged about 550,000 to 765,000 years ago.



The researchers identified 10 other genes that have variants that protect against the vascular form of dementia (APOE, AGT, SCG2, CAPN10, TCF7L2, EBF1, COX-2, CYP3A5, PPARG, and PON1). Instead of drowning brain cells in amyloid beta and tau proteins, vascular dementia blocks blood flow. The 10 genes protect against hypertension, type 2 diabetes, and cardiovascular disease. These "derived protective alleles" are found in all modern African populations, indicating that they're at least 100,000 years old.

The paper presents an intriguing hypothesis and some observations that might be consistent with an evolutionary value for life beyond young parenthood, which I'm very happy to hear. "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," summed up Dr. Ganeux.

It might be nice to develop a genetic test panel for something good for a change. "Protection against dementia" anyone?

More information: Flavio Schwarz et al. Human-specific derived alleles of and other genes protect against postreproductive cognitive decline , *Proceedings of the National Academy of Sciences* (2015). DOI: 10.1073/pnas.1517951112