REPLY TO LIU AND JIANG:

Maintenance of postreproductive cognitive capacity by inclusive fitness

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Our paper examines genes influencing cognitive decline in postreproductive humans, which arises from neurodegenerative and cardiovascular disease (1). Among these polymorphic genes, we found many protective alleles that are derived from and are unique to the human lineage. Liu and Jiang (2) add an important observation about potential effects of some of these loci earlier in life. Data from three studies indicate that these genes do not influence cognitive performance during childhood (3) or in the general population (4, 5). Our paper (1) does not address early phenotypes, as the establishment of early cognitive function and protection against late degeneration need not involve the same mechanisms. However, Liu and Jiang's (2) findings suggest that many alleles protecting cognition in elders have no strong effects on early cognition. This observation supports the hypothesis that postreproductive cognitive protection may have evolved by inclusive fitness.

The protective effects of these alleles in the elderly are not in question. As Liu and Jiang (2) mention, the association of *CD33* rs3865444 with Alzheimer's has been confirmed by multiple independent studies (6). We propose that these protective phenotypes can evolve even after reproduction ends, because elders still influence fitness of younger individuals. Cognitively intact elders are better caregivers, transmit knowledge and cultural information more reliably, and are less prone to costly behaviors or prolonged incapacitation that could burden their social groups. If alleles protecting cognitive function in the elderly are maintained by inclusive fitness, then we do not necessarily expect strong effects early in life. Indeed, a much greater force of selection on early phenotypes should overwhelm any protective effects later on (7).

The persistence of polymorphic alleles at these genes indicates that any phenotypic effects early in life must be neutral or balanced against late advantages. Uniformly advantageous alleles should be fixed by their combined effects early and late in life. Conversely, alleles with early-life disadvantages will only remain polymorphic if their effects are offset by inclusive fitness benefits. If an early deficit were too large, these polymorphisms would be eliminated by selection. There are likely many other potential protective phenotypes that do not persist because of this kind of antagonistic pleiotropy (8).

We suggest that inclusive fitness benefits passed from old to young can explain the maintenance of cognitive function in nonreproductive individuals. Although Liu and Jiang (2) provide supporting evidence, late-acting alleles could evolve by selection on any correlated phenotype during the reproductive period. Indeed, one of the variants we studied shows a balance between early and late effects. The APOE4 allele (which Liu and Jiang do not address) may protect the cognitive development of young individuals under diarrhea stress or starvation, but increases the risk of Alzheimer's decades later (9, 10). Such examples will allow us to examine the balance of early and late selective forces, and shed light on the ability of inclusive fitness to shape altruistic phenotypes and reshape life-history trade-offs, and the evolution of senescence, realizing that social, cultural, and linguistic features of humans influence the ability of elders to direct their care, but require cognitive capacity.

1 Schwarz F, et al. (2016) Human-specific derived alleles of *CD33* and other genes protect against postreproductive cognitive decline. *Proc Natl Acad Sci USA* 113(1):74–79.

2 Liu G, Jiang Q (2016) Alzheimer's disease *CD33* rs3865444 variant does not contribute to cognitive performance. *Proc Natl Acad Sci USA* 113:E1589–E1590.

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The authors declare no conflict of interest.

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