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Letter to the Editor

Letter to the Editor on "Threonine 53 in α-synuclein is conserved in long-living non-primate animals"

Dear Editor

In their article, "Threonine 53 in α-synuclein is conserved in long-living non-primate animals" (BBRC 387:602–605) Larsen and colleagues twice cite my prior work on fixed species differences in primate *SNCA* (Hamilton, 2003, Genomics 89:739–742) as proposing that fixation of the T53A substitution is an adaptation of long-lived species. This is not true. In fact, I argued nearly the opposite. The short abstract reads:

"The α-synuclein mutation Ala53Thr is associated with increased oligomerization, toxicity, and early onset Parkinson disease in humans, but 53Thr is the normal residue in other species. Comparative sequencing of *SNCA* genes shows that 53Ala marks the divergence of Old World and New World primates, in an otherwise constrained protein region. These results have implications for interpreting Parkinson disease models and *suggest that other long-lived mammals have different mechanisms to forestall α-synucleinopathy*." [emphasis added]

I explicitly point out "that the shift [A53T] *predates* hominid species whose life spans reach the mean age of onset of parkinsonian symptoms in human A53T heterozygotes," rather than being a selective adaptation for longevity and conclude:

"*The present results suggest that long-lived mammalian species that are 53T have adapted alternative mechanisms to minimize toxic accumulation of α-synuclein oligomers... Such mechanisms might include compensatory changes in SNCA that minimize 53T toxicity, altered expression of SNCA or other synucleins, altered interactions with binding partners important for toxicity, or increased turnover.* For proteins like α-synuclein whose functional or structural constraints may make them prone to aggregation, a comparative medicine approach may help to identify suppressive mechanisms that are well tolerated in vivo." [emphasis added]

While I am glad Larsen and colleagues took notice of my brief 2003 paper, I would have preferred that they understood it before using it as a straw man for their own study, which would otherwise be a welcome addition to identifying sequence constraints in synuclein genes.

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